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## ON THE GENESIS AND PHYSIOLOGICAL SIGNIFICANCE OF SPASTICITY AND OTHER DISORDERS OF MOTOR INNERVATION: WITH A CONSIDERATION OF THE FUNCTIONAL RELATIONSHIPS OF THE PYRAMIDAL SYSTEM.

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## I.—Introduction.

In a previous paper [25] certain of the reflex phenomena seen in the lower limbs in spastic paralysis were described, and their physiological significance discussed. For the first time a serious attempt was made to identify in man those principles underlying the physiological activity of the nervous system which the researches of Sherrington have revealed in the lower animals.



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In particular, certain reflex movements were described, and in the investigation of the conditioning, form, and significance of these as purposive reactions, certain general principles in the functional activity of the spinal cord in man were elucidated, and it was concluded that "analysis of the phenomena of spastic paralysis of the lower limbs in man demonstrates the close analogy existing between the physiological principles of motor innervation in animals and in man."

The allied phenomenon of spasticity, or hypertonus, associated with pyramidal lesions, also necessarily came under review, since it possesses to a large extent the same anatomical and physiological basis as the reflex movements in question—being, indeed, it was suggested, the characteristic expression of the activity of another reflex system in the central nervous system. Yet many aspects of the problem remained untouched, and a subsequent study of these was planned. During the intervening period, however, circumstances have not allowed of its completion. In the meantime the fruitful researches of Head and of Riddoch [9], [18], in the same field, have established the validity of the principles then laid down, and have also added considerably to our knowledge of the functional capabilities of the isolated spinal cord in man.

The subject may be resumed, therefore, in the hope of still farther elucidating some of the many vexed problems in the motor innervation of the skeletal musculature that yet remain for solution.

It is widely recognized, in considering the functions of the pyramidal system, and in studying the phenomena that follow its interruption, that we must take into account those other efferent paths that research, during the past two decades especially, has shown to play so essential a rôle in motor innervation. The problem therefore resolves itself into but a single aspect of the larger question of the functional relationships of the pyramidal system with the other components of the efferent system.

It is our imperfect knowledge of these, both anatomically and physiologically, that renders the problem so difficult and obscure.

Our methods of clinico-pathological and of physiological investigation into the functions of a motor path are based upon the study of excitation and destruction phenomena, and consideration will show that these methods do not provide us with simple positive and negative pictures from which we may deduce directly the functions of a single system.

To the performance of a voluntary, purposive and co-ordinated

movement go many factors. In stimulation experiments on the "motor cortex" we see a complex motor mechanism at work under the influence of an abnormally induced, crude form of hyper-activity of the predominant partner in this mechanism. Conversely, after destructive lesions, we observe it at work liberated from the control of this predominant partner and deprived of its actual co-operation.

In other words, we are studying a mutilated residual innervation, itself probably composed of several factors, and capable of resolution into simpler components.

Broadbent [2] has lucidly stated the position in terms of the Jacksonian principle: "The functions of a centre in which a lesion has occurred are suspended, and corresponding symptoms which may be called negative are observed. These, however, are not the only symptoms; other symptoms usually more obtrusive, and often infinitely more important, are produced by the activities of other centres, either (*a*) unbalanced in consequence of the absence of normally opposing activities; or (*b*) liberated from the control of higher level centres; or (*c*) intensified by attempts to compensate for the missing functions." (Super-positive activities, e.g., that of the opposite internal rectus on external rectus paralysis).

It is out of this reaction of the entire nervous system to injury of one of its component parts that we have to form our conception of the normal functions of the system which has fallen out.

As v. Monakow points out, there are three aspects from which the problem of cerebral localization may be approached. The purely anatomical localization, i.e., of tracts and cell stations, the localization of symptoms and symptom-complexes by clinical and pathological investigation of disease, and the localization of function, which is the most difficult of the three, and he concludes: "Nichts hat die Diskussion über den Lokalisation im Grosshirn so sehr verwirrt und in unfruchtbare Bahnen gelenkt, als die Nichtbeachtung der Verschiedenheit in der Fragestellung, die jede dieser Lokalisationsweisen zur Grundlage hat" [17]. Herein undoubtedly lies the peculiar danger in the acceptance of hypotheses based entirely on clinico-pathological data, and uncontrolled by physiological observations.

It will be readily admitted, when we compare the coarse undiscriminating lesions which provide the bulk of clinical and pathological material with the clean-cut selective lesions produced by the experimental physiologist, that the latter has many advantages in approaching the problem of localization of cerebral function. An approximate

localization of symptoms is often all that the clinician can hope to achieve.

Recent observations, both clinical and experimental, may appear at first sight to have dethroned the pyramidal system from its position of pre-eminence among central efferent paths. Among neurologists the grave disorders of motion seen in such diseases as paralysis agitans, the midbrain lesions described by Gordon Holmes [10], and the corpus striatum syndromes of C. Vogt and of S. A. K. Wilson [27], associated as they are with an intact cortico-spinal system, have thrown into great prominence the part played by "extra-pyramidal motor paths." To the rubro-spinal tract, in particular, has been ascribed a variety of functions, and Wilson [27] has even ventured to attribute to the corpus striatum and its primitive projection system a function of control over cortico-spinal innervation, evolutionary and phylogenetic conceptions notwithstanding.

Physiologists, too, have obtained remarkable results. Rothmann, particularly, and Schafer [19] by extirpation of the motor cortex, transection of the pyramids in the medulla and division of the lateral and ventral tracts of the cord, singly and in various combinations, have demonstrated how transient is the motor disability following interruption of the pyramidal system, and how extensive a rôle is played by other efferent paths.

Using the chimpanzee, Sherrington and Graham Brown [23] find that following excision of the "arm area" of the cortex, complete restoration of function in the corresponding limb is attained within a few weeks. Moreover, they were able to exclude a vicarious activity in this respect of the corresponding post-central or the crossed precentral cortex.

The basis of restoration of function in man after lesions of the pyramidal system is difficult to determine, both from the nature of the diseases studied and from the limitations of the clinical method. Whether return of power in these cases is due to regression of the original pathological process, and resolution of diaschisis (v. Monakow), or to vicarious functioning of other and intact portions of the nervous system (Munk), is commonly impossible of determination. Horsley's [12] well-known observation on a case from whom he had removed the arm area of the precentral gyrus indicates that in man also some degree of vicarious restoration must obtain apart from recovery due to the factors proposed by v. Monakow. Horsley concludes that "so-called volitional movements are not alone generated

from the brain through the 'motor' area or precentral gyrus, but must also be subserved by other paths." It must be admitted, however, that the alternative suggested by Horsley is not supported by the experiments of Sherrington and Graham Brown quoted above.

Two facts stand out clearly from the sum of clinical observation, and seem to indicate that supremacy of the cortico-spinal system in the efferent path, which evolutionary considerations would lead us to expect; namely, that complete paralysis of voluntary movement follows lesions of this path alone, while in "extra-pyramidal motor diseases" total loss of power is never seen. Voluntary movements may be impeded by tremor, rigidity, or athetosis, but they are not lost. There is little or no true paralysis.

It is, therefore, apparent that in any study of the phenomena of hypertonus and contracture in pyramidal lesions we cannot escape a consideration of the relationships of the pyramidal to the other efferent motor paths.

In discussing certain aspects of these problems here, particular attention will be paid to those physiological researches of Sherrington which have already given an earnest of their value to clinical neurology. It is, perhaps, not too much to say that they bid fair to renew and reinforce in English neurology the stimulus it has received from the teachings of Hughlings Jackson.

## II.—Spasticity and Decerebrate Rigidity.

### (a) *The Character of Spasticity in Hemiplegia and in Paraplegia in Extension.*

In my previous paper evidence was advanced that in spastic paralysis of the lower limbs (the upper limbs were not dealt with) there were two clinical types, the extended and the flexed. That in hemiplegia, or in any spastic paralysis due to a lesion confined to the pyramidal system, the extended type was constant, irrespective of the *degree* of pyramidal involvement. In a typical hemiplegia or lateral sclerosis of the cord the lower limbs lie fully extended with the feet plantar-flexed. The limb extensors are hypertonic, show brisk tendon reflexes and often clonus. This group of muscles also retains relatively more residual voluntary power than its antagonists, the flexors.

These, on the other hand, do not show the spasticity characteristic of the extensors, though they yield brisk tendon jerks (hamstring jerk) and show a phasic type of reflex activity, of which the flexion reflex and its

component Babinski response are the chief expression. In other words, both flexors and extensors manifest an increased and characteristic reflex activity, as spasticity in the extensors and as reflex movements in the flexors.

In severe spinal lesions we may see the flexed type of paraplegia. On analysis of this it is seen that the extensors have lost their characteristic reflex activity; while their antagonists, the flexors, show an extreme degree of reflex action, so that whereas spasticity, knee-jerks and clonus are lost, there is a flexed position of the limbs and flexor spasms of great frequency and violence. The two reflex systems, tonic and phasic, have been differently and separately affected.

Finally, it was concluded that the extended type of spastic paralysis was identical with the "decerebrate rigidity" described by Sherrington in animals, that the spastic element was the same phenomenon as the tonic extensor rigidity seen in these animal preparations, and possessed similarly a mesencephalo-spinal reflex arc; while the phasic reflex activity of the flexors, seen in both types of paralysis, was spinal in level and was the expression of the reflex activity of the spinal cord.

It was urged farther that in paraplegia in flexion we saw, in effect, the "spinal man" without the phenomena of spinal shock and isolation dystrophy, which commonly obscure and destroy the expression of spinal reflex function in man after actual transection of the cord.

This hypothesis, differing widely as it does from the views now current as to the pathogenesis and significance of the spastic element in spastic paralysis, must be considered more in detail in its physiological aspect and as to its anatomical basis before it can be regarded as proven.

Moreover, some consideration must be given to the special features of spasticity in the upper limbs in man in relation to their altered functions compared with those of the lower limbs.

### (*b*) *The Physiological Analogy between Spasticity and Decerebrate Rigidity.*

From this aspect the spastic lower limb in a case of hemiplegia presents a close resemblance to the hind limb of the decerebrate animal. The spasticity has the same selective incidence in the limb extensors (including plantar-flexors). In both the hypertonic muscles reveal their tone, not on palpation, but on passive stretching. The "clasp knife" character of spasticity finds a counterpart in decerebrate rigidity [5],

and in both instances de-afferentation abolishes the rigidity (Förster's operation in man).[1]

Whether spasticity in man presents to the same degree the plastic quality described in decerebrate rigidity may be questioned. The striking modifications of attitude produced by Förster in spastic limbs indicate a certain measure of plasticity. Probably the slower development and long duration of spastic conditions in man, resulting as they do in prolonged immobility and secondary changes in the muscles, may help to diminish this quality.

It may be considered extremely probable also that the minimal metabolic activity characteristic of the muscular contraction in decerebrate rigidity (Roaf, Bayliss) would be found to obtain in spastic conditions in man.

As yet, it can be scarcely profitable to discuss in this connexion the dual nature of tonus postulated by de Boer, Boeke and Langelaan. The recent observations of Cobb [7] provide no evidence that decerebrate rigidity is in any way concerned with sympathetic innervation.

### (c) *The Anatomical Basis of Spasticity and of Decerebrate Rigidity.*

At first sight a serious obstacle to the identification of spasticity with decerebrate rigidity is presented by the observations of Sherrington [20] and of Weed [26], working in the same laboratory, that following unilateral decerebration the resultant rigidity is homolateral, not crossed as in hemiplegia.

According to Sherrington, the development of rigidity is somewhat inconstant after unilateral decerebration, and is mainly homolateral, and Weed obtained similar results. However, light is thrown upon this point by Thiele [24] who, using the method of successive (unilateral) coronal sections, found that rigidity appeared when the plane of the caudal extremity of the thalamus was reached, and is then

[1] Since completing this paper a lost reference has been refound, and is so apposite, and expresses so clearly what may be found in the vasti muscles in any spastic extended leg, that I quote it in full.

Discussing the plastic tone of the decerebrate animal as seen in the "lengthening reaction" of the vasto-crureus, Sherrington remarks that "when the forced flexion is begun resistance, even considerable, is felt opposing it. The extensor muscle's tonic contraction refuses, so to say, to yield. But under continuance of the strain this resistance almost suddenly subsides; the tonic contraction of the muscle abruptly gives way; the resistance from that moment onward is less; the flexing of the knee and the forced stretching of the muscle meet with little further opposition."—*Quarterly Journ. Exper. Physiol.*, 1909, ii, p. 109.

contralateral. He says: "If the transection was made far forwards in the region of the optic thalamus and the anterior corpora quadrigemina marked contralateral rigidity was produced, the homolateral limbs were scarcely at all affected and then the rigidity occurred in them later and only on manipulation of the limbs. When the lesion was made farther back in the region behind the corpora quadrigemina the homolateral rigidity was obtained with only slight contralateral. These facts point to the conclusion that the influence descending from the thalamus is a crossed one, and that the decussation takes place high up in the region of the decussation of the rubrospinal tract."

Confirming this is Sherrington's observation that decerebrate rigidity can be inhibited in a given muscle group by stimulation of an appropriate point in the crossed motor cortex [20].

Farther, since the mesencephalic excitation experiments of Thiele, Weed and others indicate the red nucleus and rubrospinal tract as the point of departure and the conductor respectively of the efferent impulses subserving decerebrate rigidity, such a crossed relationship seems inevitable. The encephalic connexions of the red nucleus are uncrossed, its cerebellar and spinal connexions crossed.

The cortical point, stimulation of which inhibits the rigidity, is that from which excitation of the antagonist of the inhibited muscle is obtained (under reciprocal innervation).

Therefore both anatomical and physiological considerations indicate that decerebrate rigidity is dependent upon removal of a crossed cerebral control.

### (*d*) *The Special Position of the Upper Limbs in Man.*

In quadrupeds the fore limbs share the locomotor function with the hind limbs, and we find accordingly, in the decerebrate animal, the same extended position in both fore and hind limbs; that is, the same incidence of the postural tone.

In man, erect and bipedal, the conditions are quite different. The upper limb has been promoted "from a simple locomotor prop to a delicate explorer of space in manifold directions" (Sherrington [21]).

There is abundant evidence that the mechanism of progression is laid down in lowest level centres, and in such a mammal as the cat is capable of functioning at birth, like the respiratory centre (Graham Brown [4]).

In this respect the upper limb in man is very differently placed. Its functions are largely acquired under the dominance of the cerebrum.

If it can be said to possess a primary inherent function it is that of embrace, grasping, and of carrying food to the mouth. In these primitive movement complexes, the limb flexors fulfil a purpose analogous with that of the extensors engaged in the postural extension reflex in the hind limb.

These *a priori* considerations gain significance when we study the attitude of the upper limb in hemiplegia. In this condition the typical position of the limb is one of flexion at all joints with adduction and semipronation. In tetanus spasms, and in the "tetanus-like seizures" of Hughlings Jackson, the arms are rigidly flexed; the legs rigidly extended.

The spasticity of the upper limbs, its incidence in the flexors excepted, resembles in all respects that found in the lower limbs.

Of no less interest is the relatively poor recovery of the upper limb in hemiplegia, when compared with that sometimes found in the lower limb in a given case. These points indicate not only that the incidence of the postural tone has changed with the altered functional conditions, but also that the upper limb is more dependent on cortical control and innervation than the lower limb, which is still engaged in its primitive locomotor function.

It is noteworthy that in the frog, in which the habitual posture of the hind limbs is one of flexion, the postural tonus is a flexor tonus (Sherrington [22]).

Perhaps the absence in the spastic upper limb of any reflex analogous with the nociceptive flexion reflex of the lower limb is another expression of the altered innervation and functional relationships of this limb in man.

The view advanced previously [25] and in this paper may, then, be summarized as follows: The spasticity of spastic paralysis as seen in hemiplegia and in paraplegia in extension is analogous with the decerebrate rigidity of Sherrington. It is, therefore, an expression of the activity of the proprioceptive system taken as a whole. This system induces a tonic reflex, which, unmasked in the decerebrate animal, has been shown to possess the significance of a postural reflex—reflex standing. In man also we see in hemiplegia a rigidity which has the same significance. However, in this instance, the upper limb shows typically an attitude of flexion; the hypertonus is resident in the limb flexors, not in the extensors as in the lower limb.

This may be traceable to the altered functions the upper limb exercises in man, and to its complete lack of the locomotor function.

## III.—Förster's Theory of the Origin of Spasticity.

Reference has been made earlier to other hypotheses of the origin and nature of the spasticity seen in spastic paralysis. No one of these takes cognizance of the principles laid down by Hughlings Jackson, or of those fundamental conceptions of the reflex activity of the nervous system we owe to Sherrington. We cannot therefore expect, nor do we obtain, much enlightenment from them.

It is to Förster that we owe the demonstration that de-efferentation of spastic muscles abolishes their rigidity. This is the basis of his operation of posterior root section, and forms the starting point of his theory of the pathogenesis of spasticity in pyramidal lesions [8].

He believes that the pyramidal tract exercises both excitatory and inhibitory functions. The latter consist in the "imbibing or sucking up" of the excess of afferent impulses which reach the ventral horn cell. He says: "If this inhibition fails, the unimpeded sensory afflux charges more and more the anterior horn cell, increases its excitability, and produces a permanent motor stream from the ganglion cell to the muscle, that is to say, the spastic contracture."

So much for causation; as for the selective incidence of the spasticity he states: "Whether this or that muscle group is subject to contracture or not depends on external conditions, and this condition consists exclusively in the degree of approximation of the points of insertion of the muscular group, or, in other words, the position of the limb in question. The muscular group, the points of insertion of which are at a maximum distance, shows no spasticity."

Three subsidiary factors in turn are invoked to determine the necessary position of the limb: the action of gravity, involuntary movements caused by sensory stimuli ("Abwehrbeugereflexe"), and the distribution of the residual voluntary mobility.

From this it follows that the incidence of spasticity, and hence the attitudes of the spastic limbs, are entirely dependent on external and capricious factors, and Förster claims that he can change the incidence of the spasticity at will by modifying the position of the spastic limb.

Against the value of these multiple and uncertain factors, the absolute constancy to one or two types, under ascertained internal conditions, of all cases of spastic paralysis is the strongest indication.

Further analysis shows that in each element Förster's hypothesis is incompatible with the facts.

The dual function ascribed to the pyramidal tract is not, it will be

seen at once, in accordance with those processes of reciprocal innervation which we know motor cortex reactions to show, nor with the modern conception of the origin and nature of muscle tone. Förster regards the latter as the functional expression of a purely spinal reflex arc. We know that this is not the case.

Further, it seems clear that the factors determining the incidence of the spasticity, and hence the attitude of the limb, are internal, not external and adventitious. Thus only can we account for the transformation of a paraplegia in extension to one in flexion. There is some evidence that passive position may have a modifying influence in this respect; Sherrington has found it so in animal preparations, but none that it is the determining factor.

This point was made the subject of investigation by Dr. F. E. Batten, at a time when I was his house physician at the National Hospital, Queen Square.

A case of infantile spastic diplegia with rigid, extended legs, adductor spasm and "scissors gait" was put up in plaster in a position of as extreme abduction as was compatible with comfort. The legs were slightly flexed at knee and hip. This position was maintained for sixteen days.

On taking the limbs out of the plaster, they were found to maintain an abducted and slightly flexed attitude. Passive adduction met with slight tonic muscular resistance, and Förster's conclusion seemed confirmed, but within two weeks the original adducted and extended position had spontaneously returned with all its old intensity. It was evident that the determining internal factors had soon overset the external and adventitious ones.

As a determinant of attitude, gravity can scarcely be invoked as responsible for the flexed adducted attitude of the arm in hemiplegia, which indeed is a permanent defiance of gravity, nor in hemiplegia do the "Abwehrbeugereflexe" determine the incidence of the spasticity.

They are, as I have shown, due to the activity of a reflex system involving other muscles than those engaged in the maintenance of reflex tone. Reflex movements and spasticity stand in no causal relationship one to the other, but are both the result of loss of cerebral control over lower level reflex systems.

Involved in Förster's theory is still another subsidiary factor introduced to account for the form and genesis of the "Abwehrbeugereflexe"—indeed, the multiplicity of the causes invoked to account for a set of phenomena readily traceable to a single cause that constitutes the inherent weakness of all the current hypotheses on this subject.

## IV.—The Proprioceptive System and the Cerebellum.

### (*a*) *The Position of the Cerebellum in the Proprioceptive System.*

If we accept these conclusions, it will be seen that the importance thereof lies not alone in the elucidation of the origin and significance of a group of symptoms, but even more in the fact that in these phenomena we are studying the activities of one of the "extra-pyramidal motor systems."

It is important, therefore, to elucidate as far as possible the anatomical basis of these symptoms. The question of the crossed relation of the cerebrum to the rigidity has already been discussed.

The reflex arc itself in decerebrate rigidity we may construct with reasonable certainty from the observations of Sherrington, Thiele and Weed. The afferent impulses upon which the rigidity depends arise in the muscles concerned, reach the cord by the posterior roots and pass up in the ventrolateral column on the same side of the cord. From the researches of Weed it seems extremely probable that the cerebellum is an important and essential link in the reflex arc. There is evidence that, following the course taken by the spino-cerebellar fibres of Gowers' tract, the afferent impulses reach the cerebellar cortex via the superior cerebellar peduncles. The efferent arm of the arc leaves the cerebellum by the same route, its descending arm being cerebello-rubrospinal.

This is of some interest in view of the functions which various clinical observers have ascribed to the rubrospinal tract.

Although in man we can scarcely hope to obtain such extensive information as to the separate links in the reflex arc of which spasticity is the functional expression, certain significant facts are known. That it arises in the muscles themselves is seen by its abolition when these are de-afferented (Förster's operation), and, as I have pointed out in my previous paper, the efferent link of the arc is resident in extra-pyramidal paths.

There are indications, too, that the cerebellum is an essential link in the chain, and upon the whole it seems reasonable to suppose that just as spasticity resembles decerebrate rigidity in character and incidence, so its anatomical substratum is the same.

### (*b*) *The "Corresponding Opposite" of Spastic Paralysis.*

The condition of maintained muscle tone in the decerebrate animal is regarded by Sherrington as one expression of what he has called the

proprioceptive system. The physiological significance of this, so comprehensively described by him in many papers, need not now be discussed except in so far as concerns the cerebellum, the position of which in this system is of primary importance in our present connexion.

Sherrington's conception is that the labyrinth is the proprioceptor of the head segments, and that the cerebellum may be regarded as the central nervous mechanism of this receptor, which, like the other receptor organs of the head, tends functionally to dominate the segmental receptors.

Concordantly with the fact that the labyrinthine proprioceptors are the most important, the central mechanism is an organ of high complexity. It receives the vestibular nerves and also internuncial paths from all the segmental proprioceptors and is "the chief co-ordinative centre, or group of centres, of the reflex system of the proprioceptors" [21].

Proprioceptive reflexes are typically secondary to exteroceptive reflexes, which they may reinforce or inhibit, and in restoring the posture transiently overset by phasic exteroceptive reflexes, they have also a compensatory action. The proprioceptive system, then, maintains and regulates tonus in the "antigravity muscles."

In Sherrington's original observations on the decerebrate animal he found that ablation of the cerebellum did not abolish the rigidity [20].

This is scarcely what would have been expected in view of the position in the proprioceptive system of this organ. That its removal should leave the reflex system, of which it is at once the great co-ordinating centre and a component part, in unimpaired function is difficult of comprehension.

It is very significant, therefore, that, in agreement with the observations of Horsley [13], Weed finds that ablation of the cerebellum and procedures calculated to impair its activity abolish an established rigidity, and prevent the appearance of rigidity on subsequent decerebration [26], and he concludes that the cerebellum forms a very important, if not essential, pathway for the afferent impulses from the limbs and trunk concerned in decerebrate rigidity; and Sherrington [22], discussing these experiments, states that they indicate that "the cerebellum commonly lends this reflex a large amount of support and refined adjustment."

If we may conclude that the cerebellum is an essential link in the proprioceptive reflex arc we are brought nearer again to Jackson's

conception of "cerebellar influx," even though we now recognize the reflex origin of the rigidity.

But we may still follow Jackson with advantage in our consideration of this problem, and in doing so the purpose of this digression into the functions of the proprioceptive system will become apparent.

One of Jackson's observations was that "certain cerebral and cerebellar maladies may be contrasted and compared with one another as being complementary inverses (corresponding opposites)."

Beginning, then, with our conception of the origin and nature of spasticity, we may endeavour to determine on theoretical grounds what the "corresponding opposite" of spastic paralysis would be.

On the negative side, we should expect to find atonia in previously tonic muscles from loss of the proprioceptive postural tonus, while on the positive side we should anticipate certain disorders of voluntary movement depending, also, on the lapse of this involuntary reflex mechanism of co-ordination.

Further, assuming that the cerebellum is an essential pathway in the reflex arc which is responsible for the spasticity in hemiplegia, and of which the rubrospinal tract appears to be the descending limb, it seems reasonable to suppose that cerebellar disease, in that it would constitute a breach in the reflex arc of the proprioceptive system, should provide us with this "corresponding opposite" of spastic paralysis. In effect, this corresponding opposite would be the equivalent of an extrapyramidal motor disease, since it would put out of action the cerebello-rubrospinal path.

We cannot but be struck, therefore, by the completeness with which, in fact, cerebellar disease fulfils these conditions.

In this connexion the comprehensive study of acute cerebellar lesions by Gordon Holmes [11] forms an admirable standard by which we may compare the two. On the negative side we see a pronounced atonia of the musculature. Loss of power is minimal and transient: "an asthenia rather than a paresis."

On the positive side there is the composite picture of cerebellar ataxy.

Now although Sherrington's conception of the position of the cerebellum as a reflex centre may in the abstract have found acceptance, yet it cannot be said that it is as a link in the proprioceptive system that this structure is commonly regarded by neurologists in discussing its symptomatology.

Yet clearly this aspect is of the greatest importance to an appreciation of the physiological significance of cerebellar disease.

It is interesting to speculate in how far we may expect voluntary movements to be disordered when the reflex activity of the proprioceptive system considered as a whole is in abeyance.

Gordon Holmes expresses the view that while atonia may account for the "rebound phenomenon" described by him and Grainger Stewart, it cannot produce the various components into which the cerebellar ataxy has been divided. It is clear that unless we adopt the modern conception of muscle tone, that we owe to Sherrington, we cannot readily correlate atonia with the ataxy of a cerebellar lesion. Yet in the light of this conception the matter seems less obscure.

The reinforcing, inhibiting and compensatory functions exercised by the proprioceptive system in respect of phasic exteroceptive reflexes have already been referred to, and it becomes apparent that in every voluntary co-ordinated movement the tonic postural reflex is an integral and essential element. There is, to use Jackson's phrase, "a perfect co-operation of antagonism" between the phasic and the underlying tonic elements in the innervation.

The atonic musculature of cerebellar disease is one from which this essential element in co-ordination has fallen out, and all movements carried out by it lack those elements of co-ordination we have mentioned, reciprocal innervation is necessarily overset, and we may regard the atonia and the ataxy as the negative and the positive expressions respectively of the same defect.

As I have suggested earlier, several factors go to the performance of a co-ordinated voluntary movement. Some of these are purely reflex and entirely subconscious. Such, for example, is the reflex mechanism under discussion. These various mechanisms cortico-spinal innervation regulates and throws into action. Should one of them fall out, voluntary innervation must of necessity be disordered, for the individual has voluntarily to compensate for and to reproduce this unconscious element in his co-ordination.

He is like a man mounted on a bicycle for the first time, and he comes similarly to grief.

We may, therefore, see in an interruption of the proprioceptive reflex arc an explanation of the atonia and of the motor disorders of cerebellar disease.

Whether the resolution of cerebellar ataxy into such components as asynergia, dysmetria, decomposition of movement and tremor has other than a purely conventional value is somewhat open to question, if this view be correct. It seems probable that they are better

considered as passing aspects of a single defect than as distinct and separable defects.

The somewhat arbitrary dissection of cerebellar ataxy into numerous and often overlapping components might even be regarded as calculated to obscure its underlying significance, since, as Sherrington points out, fractional reactions are always more difficult of interpretation than wider and more extensive movement complexes.

To summarize: Viewed in the light of Jackson's teaching and of the physiological researches of Sherrington, there appear good grounds for regarding the cerebellum as an important link in the reflex arc subserving the rigidity of hemiplegia. We may, then, look for the "complementary inverse" of spastic paralysis of corticospinal origin in lesions involving the cerebellum. Both clinical and experimental observations demonstrate how completely these lesions may produce such a contrasted picture.

In that the cerebello-rubrospinal path appears to be the efferent limb of the proprioceptive reflex arc, we may regard the motor disorders following its inactivity, which cerebellar disease entails, as an example of an extrapyramidal motor disease.

## V.—Associated Movements in Hemiplegia.

There is still another feature distinguishing spastic paralysis from its "corresponding opposite." In hemiplegia there is seen a group of involuntary phenomena known as associated movements (Syncinésies, Mitbewegungen). These form no part of the symptom-complex of cerebellar lesions, and it seems reasonable to regard them as probably arising in the same mechanism that is responsible for the production of spasticity in hemiplegia.

Innumerable classifications and descriptions of these are to be found in the literature of neurology, but very little profit is obtainable from their study. Reference to the large number of papers on this subject that have appeared in the *Revue Neurologique* during recent years reveals the fact that movements of widely differing origin and character have been included within the term "syncinésies," and we readily recognize certain of the reflex movements studied in my previous paper. In their full and minimal forms both flexion and crossed extension reflexes find place in these tedious classifications, which do not even agree as to the morphology of the movements they describe.

It seems better, therefore, to approach the question from the point

of view hitherto adopted in this paper, than to do so trammelled by conflicting hypotheses that have but one point in common—that they completely ignore all that we have learned in recent years of the physiology of the nervous system.

An essential condition of the production of an associated movement is a voluntary or involuntary movement of the normal half of the body. Any forceful movement of one of the normal limbs, or such involuntary bilateral movements as yawning or coughing, will in a typically spastic hemiplegia evoke an associated movement on the hemiplegic side. In the spastic upper limb, following a strong grasp of the normal hand, we see a slow but powerful flexion at elbow and distal joints, sometimes associated with elevation and abduction at the shoulder. More rarely an equally slow, maintained extension of the limb occurs, with extension and fanning of the digits.

Throughout the series of cases of hemiplegia that formed part of the basis of my previous paper, I was unable to satisfy myself that there was any constant relationship between the form of the voluntary movement and the involuntary crossed movement it evoked. The two were neither constantly symmetrical nor constantly opposite in character; voluntary extension of the normal limb was as often followed by associated flexion as was voluntary flexion.

In a given case the form of the associated movement varied but little whatever the form of the voluntary movement evoking it.

Noticeable, however, was the fact that such a bilateral movement as yawning usually produced extension of the upper limb with fanning of the digits as associated movement, and the conclusion seemed justified that *crossed* associated movements of the upper limb were usually flexion, and that following *bilateral* movements associated extension predominated.

In the lower limb an increase of the extensor rigidity was the usual associated movement. Here, as in the upper limb, the involuntary movement bore no particular relationship as to form with the voluntary movement. No definite evidence of a progression type of movement was obtained.

Nor is it easy to say whether these movements show any degree of co-ordination; that is, of reciprocal innervation. Such information as is obtainable from palpation would incline me to answer this question in the affirmative. Many writers state that the muscular contraction is global, involving all the limb muscles, attitude being

determined by the more powerful group. How they reach this conclusion is not indicated.

Clinically this point is difficult of determination in the upper limb, where these movements are best studied.

A feature of associated movements is their slow *crescendo* development, and their equally slow recession when the evocative movement has ceased.

It would be easy to follow precedent in the study of these movements and to subdivide them into symmetrical and asymmetrical, or, into global, co-ordinative and imitative (Marie and Foix [16]), and so on, and to evolve a separate pathogenesis for each type (herein also following Marie and Foix).

But, as I have observed earlier, analysis of this type is as apt to obscure the issue as to throw light upon it. To endeavour to trace the varying forms these movements take to a common source seems a more profitable procedure than to subdivide and classify them, and to devise an hypothesis for each.

Whether symmetrical or asymmetrical, flexor or extensor, these movements consist in *accessions of tone* into muscle groups for the most part already hypertonic, but occasionally, as in associated extension of the arm in hemiplegia, into muscles not previously tonic.

It is in this sense, rather than as movements, that I would consider them.

If we turn to the consideration of the decerebrate animal, we find that excitation of the red nucleus area on the cut surface of the midbrain evokes characteristic reactions (Thiele, Weed, Graham Brown), whether the animal be cat or chimpanzee. The typical reaction is flexion of the homolateral fore limb and crossed hind limb with extension of the crossed fore limb and homolateral hind limb. Less commonly bilateral extension or flexion may be elicited, and throughout a series of observations on a single preparation variations of this kind may occur.

Characteristic of these movements is their slow initiation and recession. Thiele [24] says that these movements require stronger stimuli for their elicitation than do movements obtained by stimulation of the cut surface of the pyramids, and are much slower and coarser than these.

In the chimpanzee Graham Brown [3] finds that "these movements having attained their maximum tend to be maintained long after the cessation of the evocative stimulus."

Stimulation of a single red nucleus area produces bilateral movements.

It seems possible that in these coarse transient modifications of the rigidity we see a deformed expression of the posture regulating functions of the reflex arc of the proprioceptive system, elicited under crude excitation of the red nucleus, and not associated with the cerebral co-operation and control normally present in the intact animal.

Now though it must remain at present in the realm of speculation, I venture to suggest an analogy between these red nucleus reactions and the associated movements of hemiplegia.

Sherrington has shown that when a limb is employed in any active movement or series of movements, it is a function of the proprioceptive system to maintain the rest of the skeletal musculature in an adequate posture by a widespread synergic action of the musculature it controls. This involves muscles of both halves of the body equally, though not necessarily in symmetrical attitudes.

In the intact individual this is carried out under the co-ordinating and regulating activity of the cerebrum : a bilateral cortical control.

If, as in hemiplegia, one cortico-spinal path is out of action, then control over the crossed postural reflex is in abeyance, and on voluntary movements of the intact half of the musculature, especially forceful movements, such as demand widespread synergic fixation, there occurs the usual bilateral postural adaptation through the action of the intact proprioceptive reflex system. Freed from cerebral control on the paralysed half of the body, this is manifested as a crude associated movement, which thus consists in a transient modification of the spasticity.

If the view adopted here of the nature of spasticity be correct, such a phenomenon as associated movement is a reaction of the postural reflex system that might have been foretold.

In this way associated movements after crossed voluntary movements, and after bilateral involuntary movements such as yawning, are readily comprehensible. Their origin and character are both in accord with such an hypothesis.

## VI.—Three Components in Motor Innervation.

So far we have considered the activity and interrelationships of three of the components in the motor innervation of the skeletal musculature: cortico-spinal, mesencephalo-spinal (proprioceptive system) and spinal (also a reflex system).

In spastic paralysis we have a composite picture in which the voluntary cortico-spinal element is wanting. In cerebellar disease, it

was submitted, the proprioceptive system is in abeyance, while, as was indicated in my previous paper, in paraplegia in flexion and in the symptom-complex of complete transverse cord lesions we have solely the residual spinal reflex activity.

With regard to the last named, paraplegia in flexion was identified as the expression of purely spinal reflex activity, free from the obscuring effects of spinal shock and isolation dystrophy.

This view has since received conclusive proof in the study of cord transections from gunshot wound by Head and Riddoch, and by Riddoch separately in a parallel research. By what must have been an unexampled care of their patients, these observers were able to minimize the effects of spinal shock and to retard the development of dystrophic changes, and they have been able to observe well-developed spinal reflexes, protective, locomotor, visceral and procreative in character, whereas in my more limited observations I was only able to detect minimal traces of the nociceptive flexion reflex.

They have proved for man, therefore, what Sherrington has been able to demonstrate for animals, that " spinal reflex movements suggest fairly obvious protective, procreative and visceral functions on the one hand, and on the other the main movements of the progression habitual to the animal. They seem to refer to stimulation of nociceptive or sexual skin nerves, or visceral afferent fibres as though initiated by these."

In this connexion it is interesting to recall an observation of Broadbent's in 1903, which subsequent research has abundantly justified: " I do not think the human cord is inferior in its essential endowments to that of the frog, and although it loses its independence by its subordination to higher centres it retains in my opinion all its potentialities " [2].

### *The Supremacy of the Cortico-Spinal System.*

Deferring for the moment the consideration of other probable components of the efferent path, we may draw some conclusions as to the supremacy of the cortico-spinal component from our study of those already discussed. Their relative position seems accurately stated according to Jackson's conception of " levels " in the nervous system: The cortico-spinal system appertaining to the middle level, and the proprioceptive and spinal reflex system to the lowest evolutionary level.

A similar conception is expressed by Sherrington. Tracing the development of the cerebrum under the influence of the distance

receptors, visual, auditory and olfactory, he has indicated the predominant position of these receptors and of their central nervous mechanism, the cerebrum, as the "great inaugurators of reaction" and the "preponderant directive influence over the whole nervous system." He says: "The rest of the animal, so far as the motor machinery goes, is but the servant of them" [21].

The pyramidal tract is the path by which this motor machinery is controlled by the cerebrum, in man at least. *Loss* of voluntary power can be produced by its interruption, and by this alone, and not by that of subordinate components of the efferent path. Destruction of these can only produce *disorders* of voluntary movement.

The genesis of some of these disorders we have yet to discuss, but the point I would raise now is that because a negative lesion of an extra-pyramidal path "allows" tremor, ataxy, or rigidity, we must not conclude therefrom that such a path exerts a controlling or inhibiting function with respect to cortico-spinal innervation.

The falling out of a subconscious reflex mechanism—proprioceptive or otherwise—must of necessity disturb co-ordination, simply because the nervous mechanism through which cortico-spinal innervation produces its effects on the musculature is defective. To conclude with certain writers that cortico-spinal innervation is controlled or "steadied" by efferent systems of lower level, that is, of subordinate physiological position, is to reverse our conceptions of evolution in the nervous system, and to miss the true significance of the motor disorders in question.

## VII.—On the Tremor-Rigidity Syndrome of Paralysis Agitans and other Organic Cerebral Lesions.

A certain physiological significance has been revealed in the positive symptoms studied in the preceding chapters of this paper.

The three symptom-complexes described may be regarded as examples of dissolution in the middle and lower levels of the nervous system, in each of them one or other integrative element having fallen out of its appropriate evolutionary level.

The analysis of these phenomena was largely based on indications offered by the experimental physiology of the nervous system, above all by the work of Sherrington.

When we pass to the consideration of those other disorders of motor innervation—athetosis, chorea, and the tremor and rigidity characteristic of paralysis agitans and of certain basal and midbrain lesions—we

find ourselves in much more difficult country. Here physiology offers us no direct and unequivocal indications.

It is not proposed to consider these disorders at length in the present paper. Since the analysis of them by Gordon Holmes in 1904 there is little that is new to be said, nor can we yet indicate their pathogenesis or their significance, physiologically considered, with any certitude.

Yet we may select two of the most extensively studied of these for a brief general consideration from the point of view hitherto adopted here.

The couple, tremor and rigidity, seen in paralysis agitans appears to present the same characteristics and to be identical with that described in the midbrain lesions analysed by Gordon Holmes, and that occurring in the corpus striatum syndrome (progressive lenticular degeneration) of Kinnier Wilson.

The tremor in question has been defined by Holmes as a rhythmic involuntary oscillation of a limb or a part of a limb due to the alternate contractions of one group of muscles and its antagonists.

The rigidity characteristic of these conditions differs entirely from that following hemiplegia in being diffuse in its incidence and uniform in character throughout the whole range of movement. One might adapt an expression used by athletes and describe the victim of this condition as "muscle bound." To the significance of these features it will be necessary to return later.

It is true that these symptoms have been localized to certain more or less circumscribed areas of the brain, but it is a long and as yet untrodden path, from their localization as symptoms to their identification as expressions of function, or, in other words, to the determination of the functions of the organs in which disease has evoked them.

We may agree in regarding them, following Jackson's teaching, as positive symptoms and due, therefore, to the disordered activity of intact centres unbalanced by reason of functional defect in other systems or centres. (Perhaps it might be more precise to say that they represent the algebraical sum of the activities of several centres, one or more of which are functioning subnormally or not at all, while the rest are correspondingly superactive.)

In an attempt to determine the motor centre, or centres, which are acting excessively and irregularly and so producing these symptoms, we may derive some assistance from our earlier observations.

In studying the spasticity and reflex movements in hemiplegia and

in the two types of paraplegia, we noted that, although exaggerated and uncontrolled phenomena, they yet bore a clear imprint of their origin and their physiological significance, and *in this respect they were characteristic of the reflex systems in which they arose.* Thus, spasticity in hemiplegia, distorted expression of proprioceptive reflex activity though it be, yet shows the fundamental characters of a co-ordinated purposive reflex activity that betray its origin. This is also true of the reflex movements we studied.

In the tremor and rigidity of paralysis agitans we can as yet see no such physiological analogy. They appear purposeless and inherently pathological.

Let us consider the rigidity from this point of view. It clearly does not arise from the activity of the proprioceptive system, which we have regarded as the source of the spasticity of hemiplegia. We have studied this system, both clinically and experimentally, in states of exalted and of depressed activity, and it has revealed nothing comparable with this diffuse rigidity, which shows no germ of co-ordination whatever.

From the fact that the cortico-spinal system is intact in these diseases it has been supposed that its overaction produces both tremor and rigidity. Thus, Gordon Holmes [10], discussing them as they arise in certain midbrain lesions, concludes that they are due to a negative lesion of the cerebello-rubrospinal path, which he suggests normally exercises a co-ordinating influence on cortico-spinal innervation. When this fails cortical overaction produces tremor.

Wilson [27], from the study of progressive lenticular degeneration, advances a very similar view. The basis of his hypothesis is the localization of these symptoms (among certain others) in a bilateral degenerative lesion of the lenticular nucleus and its projection system.

He concludes that: "(1) The corpus striatum exercises a steadying effect on the action of the cortico-spinal system. (2) This is effected either by the lenticulo-rubrospinal system, or more indirectly via the optic thalamus and its cortical connexions. (3) When this influence is impaired pyramidal function is affected in its turn, and is seen in hypertonicity or rigidity, as well as in tremor or voluntary movement. . . . (8) Tremor is due more particularly to failure of function of the lenticulo-rubrospinal system. (9) Hypertonicity or rigidity, due to defect of the 'inhibitory' action of the corpus striatum, is possibly associated with impairment of impulses from that body via

the optic thalamus to the cerebral cortex." This, he adds elsewhere, "makes the cortical motor cells react in such a way that one of the results is increase of tonicity of all the muscles innervated by the pyramidal tract."

Certain difficulties meet us when we consider these hypotheses in the light of conclusions reached earlier in this paper.

Considering first the negative aspects of these views, we note with Gordon Holmes [10] that "the cerebello-rubrospinal path is one of the most definite and direct routes by which the cerebellum may influence the lower motor centres." We should therefore expect its interruption to produce a clinical picture more or less closely resembling that of a cerebellar lesion.

If this path be the efferent link, as we have supposed, of the proprioceptive reflex arc, it is surprising that its interruption should be followed not by atonia and ataxy, but by tremor and rigidity.

In midbrain lesions there must always be difficulty in determining which, among the several paths necessarily involved by an extensive lesion in this crowded thoroughfare, really underlies the symptoms resulting, and we cannot exclude the possibility of some other local source than that suggested by Gordon Holmes.

On the negative side Wilson's hypothesis suffers from a certain vagueness and lack of precision in its enunciation. We do not know precisely what may be comprehended in "a steadying effect." We cannot readily express this conception in physiological terms. It must, at least, include what we know as "reinforcement" and "inhibition." Phylogenetically, the corpus striatum is much older than the cortico-spinal system, and must therefore have assumed this new function of control over the latter quite late in the evolutionary history of the nervous system.

From what has been said earlier of the dominance of the cerebral cortex and its projection system, such a view of the function of a primitive and physiologically depreciated organ as is the corpus striatum can scarcely be maintained.

On the positive side there are certain objections to regarding a diffuse muscular rigidity as the expression of a cortical overaction, nor is any light thrown on the subject by such a vague general statement as that "the motor cortical cells react in such a way that one of the results is tonicity of all the muscles innervated by the pyramidal tract" (Wilson).

Recalling Jackson's conception of "cerebral influx," as changing

and not continuous, and Sherrington's observation that cortical reactions are phasic, and not tonic, and, moreover, that they exhibit reciprocal innervation, and, considering also that the motor cortex discharges of Jacksonian epilepsy are clonic, we shall find it hard to recognize in a rigidity involving the whole skeletal musculature indifferently, even the distorted expression of cortical activity. For, if this is so, then cortical action is altered not only quantitatively, but also qualitatively.

We are not helped at all by supposing that "rigidity is tremor run together," and that tremor is a phasic activity reminiscent of cortical action. For *if we accept the definition that tremor is due to alternating contraction of antagonistic groups of muscles, then this rigidity differs qualitatively from tremor*, since the rigidity seen in paralysis agitans exhibits no such trace of reciprocal innervation.

Another objection to the theory of "cortical overaction" is that these symptoms do not depend so entirely on voluntary innervation for their appearance—though they are naturally modified by it—that we are justified in saying that they have no other source.

We may conclude, therefore, that the view attributing the tremor and rigidity under discussion to uncontrolled cortical action is not established, and is contra-indicated by such knowledge as we possess of the normal activity of the motor cortex.

It would take too long to analyse the theory elaborated by Ramsay Hunt [14] to account for the paralysis agitans syndrome. The hypothesis is quite incompatible with what we now know of the physiology of such reflex acts as progression and muscle tone, and, therefore, the the theory of the functions of the corpus striatum, erected upon the localization of these symptoms to a degeneration of this structure in a case of juvenile paralysis agitans, cannot be entertained.

There is absolutely no meaning in such a statement as that "retropulsion" in paralysis agitans is due to "attempting to walk under the guidance of the cortical and cerebellar mechanisms without the safeguard of the corpus striatum, which normally regulates such acts." We know that there is a perfectly co-ordinated mechanism for this movement complex quite apart from the corpus striatum, while, on the other hand, there is no evidence that this organ has anything to do with it; while the naive creation of "an inhibitory tremor centre" in the hypothalamic region, which, when liberated from the control of the diseased corpus striatum, contrives in an unaccountable manner to *produce* the tremor of paralysis agitans, is perhaps, the most amazing feature of this "contribution to the functions of the corpus striatum."

It appears then that we have but achieved an approximate localization of the diffuse rigidity and tremor of these diseases. Nor can we form any conception of what may be the basis of the frequent, but not invariable, association of these two symptoms.

The considerations put forward in this chapter, whether subsequent research justify them or no, emphasize the great difficulties that surround the elucidation of these interesting but obscure phenomena.

The observations of v. Monakow, quoted in the first chapter of this paper, indicate the dangers which beset the neurologist in his study of these problems, and the necessity of correlating his clinical observations with those experimental results with which physiology is steadily enriching our knowledge of the functions of the nervous system.

## APPENDIX.

### Cortical Lesions and Spasticity.

From clinical and experimental sources come several indications, as yet imperfectly understood, that a pure cortical lesion of the pyramidal system often does not produce spasticity as an accompaniment of the loss of power.

They suggest the possibility that in the cerebral lesion underlying, for example, a typical spastic residual hemiplegia, analysis may ultimately reveal a second component. That is, that in addition to a negative lesion of the cortico-spinal path, interruption of another descending path may be concerned in the production of spasticity. Such a path need not necessarily be cerebro-spinal.

Among these indications we may cite those cases, long familiar to neurologists, of hemiplegia in which paralysis and hypotonus are associated. Bergmark [1] in particular has studied this question and concludes that "cortical lesions do not produce definite increase of the reflexes or the typical late contracture found in hemiplegia of capsular origin." Monakow has observed that in cerebral lesions spasticity is marked in proportion as the lesion is situated caudally.

Thiele [24] records that decerebrate rigidity is not produced by successive coronal sections of the hemispheres until the plane of the caudal extremity of the thalamus is reached, and he suggests that the inhibitory influence, to removal of which the rigidity is due, arises in this organ. We know also from Sherrington's observations that excision of the motor cortex in the ape does not produce rigidity in the limb affected. Weed [26] believes that the inhibitory influence arises in the cortex,

and he was able to locate in the mesial anterior portion of the internal capsule a spot, stimulation of which caused inhibition of the rigidity in the decerebrate animal, and he followed this area down into the mesial $\frac{1}{3}$ of the crus. The area in question was not occupied by pyramidal fibres, as stimulation showed, but occupied the position taken by the fronto-pontine fibres. Traced further, the path was found to reach the cerebellum by the opposite middle peduncle.

In connexion with this interesting observation, the phenomenon of tonic innervation ("tonic preservation") assumes a new significance. This condition has been recently dealt with in a paper by Kinnier Wilson and the present writer [28]. It is associated with lesions of the intermediate-precentral cortex. Campbell [6] has shown that the fronto-pontine fibres arise in this histologically differentiated area of the cortex.

Finally, there is the observation of Marie and Guillain [15], which may or may not be germane to the question, that descending pyramidal degenerations differ in volume and form according to whether the causative lesion is situated in the hemisphere or in the subthalamic region or brain-stem. They conclude that there are pyramidal and para-pyramidal fibres in the more extensive descending degenerations. The latter they speak of as, "à côté du faisceau pyramidal sans appartenir à ce faisceau d'origine corticale."

No conclusions are suggested from these separate observations, which are merely indicated. Whether their significance is that there is a double negative lesion underlying spastic paralysis, or no, cannot yet be decided. In any case such a development would not affect the general principles advanced here.

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# THE PATHOLOGICAL EXAMINATION OF FORTY INTRACRANIAL NEOPLASMS.[1]

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## Introduction.

The opportunity was recently offered on the reopening of the Pathological Laboratory of the National Hospital for the Paralysed and Epileptic, after a temporary closure due to the war, to examine, at the same time, a number of specimens of intracranial neoplasms which had collected there, brought from the operating theatre and the post-mortem room. To these have been added a considerable number which came to the laboratory while the examination was being carried on, bringing the total up to forty in all.

It was found impossible to examine some of the older tumours owing to imperfect preservation, so that any statistics given below are only roughly those of a consecutive number of intracranial growths.

In three cases the tumours affected the spinal cord as well as the brain, but tumours affecting the cord alone have not been included. Those cord tumours that have been examined were not of any special interest, and do not throw any light on any of the problems which the present series of intracranial tumours has raised.

The investigation of these tumours has been undertaken purely from the pathological side, and where clinical notes are included it is only to give some idea as to the age and rate of growth of the tumour.

Beyond that no attempt has been made to link together the clinical symptoms and the pathological findings.

The chief object of the present report is to make some attempt, by the investigation of a fairly large series of tumours of the brain, to clear up some of the anomalies of nomenclature which are found everywhere in the literature dealing with the subject, and to discuss, in relation to the findings in the cases examined, the nature of certain groups of tumours peculiar to the nervous system.

The present moment is a particularly favourable one for the purpose,

[1] Report to the Medical Research Committee.

as recent work has brought to a head the old controversy associated with the names of Virchow, von Recklinghausen, and Durante, and although it is still far from being decided, opinion seems to be coming round to accepting Verocay's term "neurinoma" for the tumours which Virchow called "neuromata," von Recklinghausen "neurofibromata," and Durante "segmentary neuromata."

There has also been a considerable amount of recent work on nerve-cell tumours, "ganglio-neuroma," "neuroblastoma," and the like, both of the central and sympathetic nervous systems. And while the present series only contains four neuroblastomata, certain comparisons can be made between these and between them and other tumours of nervous origin, more favourably than when they are examined by ones and twos as is most usual in the literature.

A neuro-pathological laboratory has thus an advantage over that of a general hospital in the number of specimens of tumour of the brain which can be collected for an examination; but it has disadvantages in that tumours of other parts of the body are seldom met with, and in this way mesoblastic tumours occurring within the cranium may not be correlated well with those occurring in other parts of the body.

To avoid this I have asked the opinion of Professor Matthew Stewart, of Leeds, on the nature of several of the tumours, and I am greatly indebted to him for his help and interest.

I desire also to record my thanks to the medical and surgical staff of the National Hospital for their courtesy in allowing me to make use of their cases, and for the help and advice which they have always readily offered.

## Methods of Examination.

A word must be said as to the methods adopted for examination. As all the tumours were fixed in 10 per cent. formalin immediately after removal from the body, it was found to be impossible to use many of the special staining methods for neuroglia and collagen fibres. As a routine, hæmatoxylin with van Gieson's counterstain was adopted as well as Heidenhain's iron-alum hæmatoxylin, which served to show up the character of the cell nuclei and processes. The latter stain was especially useful in the very cellular gliomata. All the neuroblastomata and certain of the acoustic nerve tumours were examined by Bielschowsky's silver method for paraffin blocks after pyridin. This was found to give very satisfactory results, but it was controlled whenever the consistency of the tissue permitted, by the method for frozen

sections. Where Nissl and Weigert-Pal staining was done, other nervous tissues were put through at the same time as controls.

The photographs do not represent a complete series, but are only introduced to illustrate cases of special interest, or to serve as ocular demonstrations of unusual features.

TABLE.

| No. of case | Initials of patient | Age in years | Nature of tumour | Figure | Duration of symptoms | |
|---|---|---|---|---|---|---|
| | | | | | Before admission | Before death |
| 1 | L. E. | 22 | Tuberculomata .. .. | — | 8 months | 11 months |
| 2 | L. S. | 11 | Tuberculoma .. .. | — | 5 weeks | 7 months |
| 3 | C. B. | 13 | Granuloma .. .. .. | — | 27 months | — |
| 4 | J. L. | 11 | Sarcoma .. .. .. | — | 3 months | 9 months |
| 5 | W. V. | 54 | Fibrosarcoma .. .. | — | 2 months | 5 months |
| 6 | E. B. | ? | Endothelioma .. .. | — | 12 months | 12 months |
| 7 | Mrs. M. | 36 | Endothelioma .. .. | — | 2½ years | 2½ years |
| 8 | Miss K. | ? | Endothelioma .. .. | — | ? | ? |
| 9 | A. B. | 35 | Endothelioma .. .. | — | 6 years | 6 years |
| 10 | W. B. | 31 | Multiple endotheliomata .. | 1-3 | 6 months | 9 months |
| 11 | C. D. H. D. | ? | Endothelioma .. .. | — | 2 years | 2 years |
| 12 | F. C. | 62 | Endothelioma .. .. | — | 21 months | — |
| 13 | P. W. | 43 | Endothelioma .. .. | 4 | 17 months | — |
| 14 | D. F. | 11 | Myxo-endothelioma .. | 5 and 6 | 3 years | 3 years |
| 15 | E. E. | 13 | Myxo-endothelioma .. | 7 | 4 years | — |
| 16 | P. M. | 48 | Perivascular sarcoma .. | 8 | 5 years | 5 years |
| 17 | S. S. | 9 | Perivascular sarcoma .. | 9 and 10 | 3 months | 4 months |
| 18 | C. P. | 46 | Perivascular sarcoma (malignant) | 11 | 15 months | 16 months |
| 19 | W. P. | ? | "Sarcomatosis of meninges" | 12 | 4 months | 6 months |
| 20 | A. B. | 20 | Glioma .. .. .. | 13 | 3 months | 3 months |
| 21 | W. W. | 29 | Glioma .. .. .. | 14 | 2 months | 4 months |
| 22 | A. M. | 58 | Glioma .. .. .. | — | 2 years | 2 years |
| 23 | T. C. | 22 | Glioma .. .. .. | — | 4 months | 4 months |
| 24 | Mrs. G. | 52 | Glioma .. .. .. | — | 2 months | 4 months |
| 25 | A. T. | 43 | Glioma .. .. .. | — | 6 months | 14 months |
| 26 | J. W. | 49 | Glioma .. .. .. | 15 | 4 months | 4 years |
| 27 | R. H. | 16 | Multiple gliomata .. .. | — | 3 weeks | 4 months |
| 28 | X. Y. | — | Glioma and "spongioblastoma" | 16 | — | — |
| 29 | L. R. | 24 | Glioma of pons .. .. | 17 | 4½ months | 11 months |
| 30 | L. C. | 13 | Multiple gliomata of nerve roots | 18 | 2 months | 3 months |
| 31 | W. H. | 26 | Neuroblastoma (malignant) | 19 and 20 | 6 weeks | 2½ months |
| 32 | T. H. | 35 | Neuroblastoma .. .. | 21-23 | 6 years | 6 years |
| 33 | Pte. E. | ? | Neuroblastoma (malignant) | 24-27 | 6 weeks | 3 months |
| 34 | M. B. | 26 | Ganglioneuroma .. .. | 28-33 | 2½ years | 3½ years |
| 35 | N. R. S. | 22 | Multiple "neurofibromata" | 34-38 | 6 months | 7 months |
| 36 | G. M. | 38 | "Acoustic nerve tumour" .. | 39 | 9 months | 9 months |
| 37 | E. M. | ? | "Acoustic nerve tumour" .. | — | 9 months | 12 months |
| 38 | S. E. | 43 | "Acoustic nerve tumour" .. | — | 2 years | 2¼ years |
| 39 | W. M. | ? | "Acoustic nerve tumour" .. | — | ? | ? |
| 40 | H. P. | 35 | "Acoustic nerve tumour" .. | 40 | 2 years | 2 years |

*Relative proportion, age incidence and rate of growth*—A glance at the table will show the relative proportions of the various forms of tumours encountered in this series. If a percentage is calculated it is found that tuberculomata total 5 per cent. and sarcomata 5 per cent., while granuloma only accounts for one case or 2·5 per cent. This has obviously no relation to percentage of incidence, but is due to the low rate of mortality in the granulomata and tuberculomata, and to the fact that sarcomata are more usually met with in general than in neurological hospitals. At the same time it is probably true that primary sarcoma of the brain is a rare disease.

The group of endotheliomata includes ten cases or 25 per cent., and " perivascular sarcomata " three cases or 7·5 per cent., and there is one anomalous case of meningeal infiltration which is probably allied to the endotheliomata. *Thus mesoblastic intracranial tumours form* 40 *per cent. of the present series.*

Gliomata total eleven, of which three are multiple. There are three neuroblastomata of the brain, and one ganglio-neuroma growing at the base of the brain. Thus *glia and nerve-cell tumours form* 37·5 per cent., or approximately the same as mesoblastic tumours.

Lastly, there are *six cases of acoustic nerve tumours*, one of which was multiple, making 15 per cent. of the series. There is considerable evidence that these should be regarded as of epiblastic origin.

In any case if we compare in this series forms of tumour peculiar to the nervous system with those which may occur elsewhere in the body, we find that the former total twenty-one and the latter sixteen. We must remember that even for the cases admitted to the National Hospital during the time covered by the present series, this will not represent a true proportion, as all the tumours brought from the operating theatre to the laboratory were of mesoblastic type; so that the proportion of other tumours is probably slightly higher.

These figures may be compared with those of Tooth for the years 1902 to 1911 inclusive, where in a total of 258 tumours, whose nature was verified after operation or post mortem, 40·2 per cent. were gliomata, whereas endotheliomata and sarcomata together amounted to only 22·4 per cent. and fibromata and fibro-gliomata 10·8 per cent. (these last all occurred in the posterior fossa of the skull, and all except four are noted as extra-cerebellar, so that we are safe in assuming that at any rate 10 per cent. are acoustic nerve tumours.

In Cushing's recently published monograph, his verified acoustic nerve tumours amounted to 8·8 per cent. of a series of 340 verified

tumours, excluding tumours of the pituitary gland, of which, owing to his special work on them, he had a much higher proportion than the average.

While generalizations from such a limited number of cases are unjustifiable, it is worth while noting the *age incidence and duration* of symptoms of the various forms of tumours.

Both cases of *tuberculoma* were in young subjects, aged 11 and 22 respectively, and gave a fairly short history.

The *sarcomata* occurred, one at the age of 11, and one at the comparatively advanced age of 54. In these the history was a matter of a few months.

All the cases of *endothelioma* occurred after the third decade, except the two cases of myxo-endothelioma which occurred in children of 11 and 13 respectively. The latter tumours are very closely allied to the "mixed tumours of the parotid," and resemble them also in their age incidence. In them the symptoms dated from three and four years before admission to hospital. The other endotheliomata gave histories dating back at longest to six years, and at shortest to six months (this in a case of multiple tumours of the cerebellum).

In the *perivascular sarcomata* we are dealing with more malignant tumours, but in one case the symptoms dated to probably five and certainly three years before admission. In the shortest history of the three the tumour was in the centre of the cerebellum, where it caused hydrocephalus and thus hastened the fatal termination.

These tumours thus seem to be definitely more slow-growing than the sarcomata of the dura mater, in spite of their definite malignant tendencies.

The *gliomata* of the series all gave a very short history, amounting in only one case to two years, and in the others to six months at most before admission. One case of undoubted neuroblastoma also gave a very short history, whereas another gave a history of fits dating definitely to six years before he entered hospital.

The *tumours of the acoustic nerve* were true to type in having histories of moderate length; the shortest (six months) was in a case of multiple tumours; the longest was two years.

They are obviously fairly slow-growing tumours, but their position and relations enable them to be diagnosed early, and unless relieved by operation their site quickly makes them dangerous to life.

## Discussion on the Nomenclature and Classification of Intracranial Tumours.

The present investigation was stimulated largely by the anomalies of nomenclature which have appeared and still appear in the literature of the subject. The objection to most of the names used is their reference to two forms of tissue which arise from different embryonic layers, e.g., mesoblast and epiblast. I refer to terms such as "glio-sarcoma," "fibroglioma," and "neurofibroma," which are used in such a way as to suggest that both the tissues named are essential elements in the structure of the tumour. These terms have been associated with the names of distinguished authorities, and it is therefore difficult to discard them without a full inquiry both into the reason for their adoption and the objections to their continued use.

The term "gliosarcoma" is justified by Lubarsch, who suggests that "the chief word must be determined by the morphological structure; if we can with certainty give the genesis, then indicate that by an adjective, as, for example, "endothelial adenoma," "epithelial adenoma," &c. This method of nomenclature is supported by Adami, who advises that the term "sarcoma" should be used "in a purely histological sense."

Bruns objects to the too frequent use of the term, which he considers due to the difficulty in diagnosis between glioma and sarcoma of the brain—"a reason why we often find the diagnosis 'glio-sarcoma' in the literature, either as an escape from a difficult diagnosis, or due to defective examination, as 'glio-sarcomata' *are probably very rare.*" (It is difficult to understand what is meant by the last phrase in the light of his previous remarks, and it is probably introduced in deference to contemporary opinion.)

Verocay and others have used the term "sarcomatodes" to indicate a histological picture resembling sarcoma, and the general use of the term "glioma-sarcomatodes" would give rise to much less confusion than the name "glio-sarcoma."

The term "neuro-fibroma" is countenanced by such long use that it will probably survive, at least until the histogenesis of this type of tumours is set on a more satisfactory basis. But it must be remembered that von Recklinghausen, in his second paper on the subject, withdrew the term "neurofibroma" as unjustifiable; and called the tumours simply "multiple fibromata." There seems to be no precedent or analogy to justify the name "neuro-fibromata" in the sense of fibromata growing in nerves; for according to von Recklinghausen's

theory of origin the tumours originate from the endoneurium, and cause more destruction than overgrowth of the purely nervous elements. On the other hand it is generally conceded that "neuro-fibromata" differ in histological appearances from all other fibromata, keeping to a type of their own.

The name "fibro-glioma" or "glio-fibroma" is in common use as describing tumours of the acoustic nerve. And the way in which the terms are used suggests that the writer is describing the appearances rather than attempting to define the origin of the tumour. The picture suggested is that of a tumour, parts of which are fibrous (though not necessarily formed of connective tissue fibres), while other parts resemble glial tissue. There are several analogies for the term "fibro-glioma," as meaning a glioma in which there is overgrowth of fibrous tissue, either to replace degenerated areas of the tumour, or formed as a reaction on the part of the connective tissue elements to the irritation of the tumour growth. And there is no doubt that some tumours of the acoustic nerve show such fibrous tissue increase. But it must be admitted that such is not the meaning intended by most writers on the subject; nor is it a correct description of the histological appearances of most of these tumours.

The objection to all these terms is that they convey the suggestion, whether intentionally or not, that the tumours arise from some cells of mesoblastic and others of epiblastic origin. And while it is allowed that this occurs in the teratomata, it is most unlikely that either glio-sarcomata or fibro-gliomata are teratomatous. In some cases, especially in the "neuro-fibromata" and the "fibro-gliomata," there is no definite knowledge as to the embryonic layer from which the tumours take their origin, and therefore they have been named "in a purely histological sense." But the confusion to which this method of naming tumours gives rise is evident from the multiplicity of names which have been applied to acoustic nerve tumours, in spite of the very constant histological picture which they present.

The truth of Cohnheim's "cell-rest" theory is assumed here, in so far as it holds that a tumour arises from a cell or group of cells which has been isolated at some stage of development and has remained immature and functionless. Their lack of function may lead the cells to assume tumour growth (Adami), or there may be a diminution of the resistance of the surrounding tissues to such growth (Ribbert). Probably both factors are at work. Ribbert's theory is upheld in part by the occurrence of multiple primary tumours, either of the same or

different types (see Cases 30 and 35), which suggests that at some period of growth, most usually during either adolescence or senescence, numerous "cell rests" commence active tumour formation.

It is evident from an examination of the cases in this series that one of the commonest seats for such "cell rests" is the junction of the nerve roots with the brain stem and cord—the so-called "transition zone."

It is possible that all stages in the development of a mature nerve cell or glia cell from the cells lining the neural crest may be represented in "cell rests." And the suggestion is put forward that certain

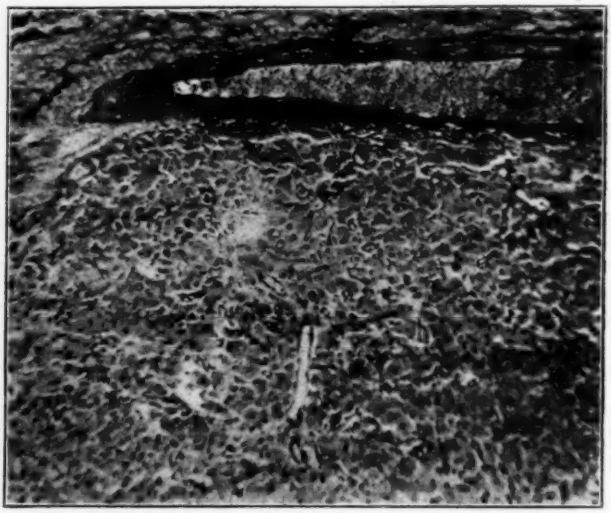

FIG. 1.—Case 13. P. W. Endothelioma of dura. The capsule contains a large vein. The tumour is formed of larger cells less clearly separated from one another than in fig. 4.

of the neuroblastomata arise from cells which have not reached the stage of differentiation into "spongioblast" and "neuroblast," and can thus give rise to cells both of the glia cell and nerve cell types. In a similar may, according to Verocay, tumours of the acoustic nerve may contain ganglion cells, as well as immature glia cells and sheath cells.

It is more difficult to understand why "multiple central neurofibromata" should be so frequently associated with endotheliomata or psammomata (see Case 35 and Verocay), if we consider the latter

tumours to be of mesoblastic origin. This might be accounted for by the theory of "diminished external resistance," and there are many analogous cases of tumours of various types arising at the same time in different organs. But when psammomata and endotheliomata are met with so frequently in conjunction with multiple "neurofibromata," the suggestion cannot be far from our minds that the association is more than accidental, and that they may not be very dissimilar in origin. Either neurofibromata may be endothelial tumours (which seems unlikely), or psammomata may be derived from "sheath cells," as is not altogether improbable (see Case 35).

### *Endotheliomata.*

The common forms of endothelioma present little difficulty. There appears to be a distinct difference both in the macroscopic and microscopic appearances between endotheliomata of the dura and of the pia-arachnoid.

*The dural form* is smoother, usually covered over by a glistening membrane, and is composed of cells of a rounded or oval shape, with, in some cases, incomplete division between the cells (see fig. 1).

*The arachnoid form* (which need not necessarily appear on the surface, and is often embedded in the brain so that only a small area presents) is rougher and is covered by a fine network of arachnoid membrane. On cut section it is more granular, and histologically it is more fibrous, being usually composed of elongated cells in whorls, with very numerous capillary blood spaces (see figs. 1, 2 and 3).

The following is a case of multiple endotheliomata of the cerebellum:—

*Case* 10.—W. B., aged 31 (physician, Dr. Batten): *Multiple endotheliomata*. Admitted March 20, 1918. Died June 12, 1918.

*History.*—Patient became giddy while on parade in October, 1917, but he had no headache or vomiting; he became worse and had a tendency to fall to the right. After admission he had occasional headaches, and attacks of vomiting, his voice was staccato, and he had general bodily weakness, but no sensory loss.

(An elder brother and younger sister died "of the same thing." Mother, aged 71, alive and well, three brothers well.)

*Macroscopic Appearances.*—On removal of the brain a yellowish softened area was seen on the posterior surface of the left cerebellar hemisphere. When hemisection was made between the two cerebellar hemispheres, an irregularly shaped cavity was seen lined with a thick yellow membrane which was easily

detachable from the brain substance. On section in the midline the cavity is seen to run from the roof of the 4th ventricle, up behind the pons and mid-brain to the pineal body, from which it is separated by a layer of normal pia mater;

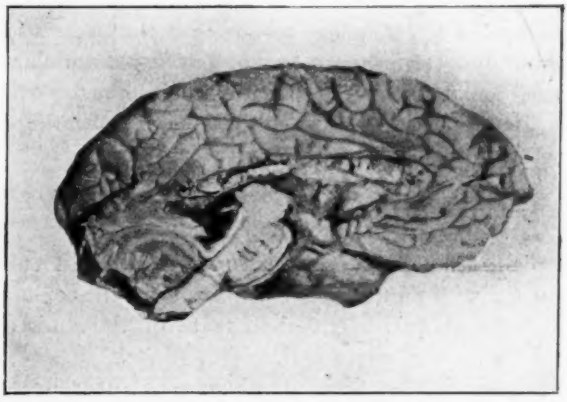

FIG. 2.—Case 10. W. B. Multiple endotheliomata. Cyst in upper part of cerebellum formed by degeneration of endothelioma.

FIG. 3.—Case 10. W. B. Multiple endotheliomata. Tumour in lower part of right cerebellar hemisphere surrounded by cyst-like space.

running from this point to the superior surface of the cerebellum it is separated from the membranes by a layer of brain tissue 4 mm. thick. On the left side it extends upwards towards the corpus callosum for 4 mm. close to the left corpus geniculatum internum. On the right side the cystic cavity runs back-

wards and outwards into the upper part of the right cerebellar hemisphere, where it is very irregular. There are four openings towards the middle line and many divarications in the substance of the cerebellum. It extends antero-posteriorly for 5 cm., and laterally for 3·5 cm.

In addition to this two tumours were found: the larger one in the left cerebellar hemisphere 1 cm. from the middle line; it is a small round tumour, clearly defined and surrounded on the upper surface by a smooth-walled cyst measuring 3 mm. in the vertical line, and 12 mm. antero-posteriorly. The cyst wall is apparently formed of smooth, slightly reddened brain tissue. The tumour itself is rounded, rather granular on the surface, and about 10 mm. in diameter.

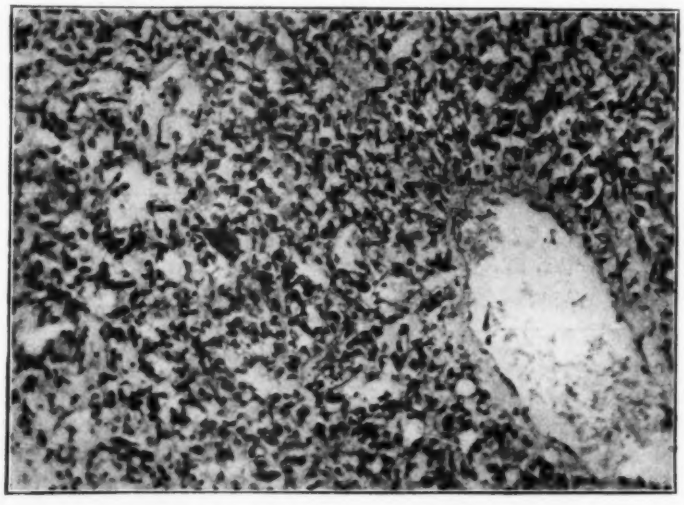

FIG. 4.—Case 10. W. B. Multiple endotheliomata. Section of tumour figured in fig. 3. Note the very numerous small blood channels. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

A similar, much smaller tumour is apparent on the right hemisphere, near the postero-inferior surface, running almost to the surface and about 1 cm. from the middle line. It measures 3 mm. in diameter. There is also a similar small rounded tumour in the left cerebellar hemisphere, attached to the cyst wall.

There are some small hæmorrhages into the pons; otherwise, except for some flattening of the sulci, the brain shows no abnormality.

*Microscopically.*—The tumour is composed of rounded collections of large epithelioid cells separated by strands of connective tissue. The cells in the masses have no very definite arrangement in whorls. They are large cells with palely staining nuclei and abundant cytoplasm; often two or three cells are joined together, forming a kind of syncytium. In other parts of the tumour

FIG. 5.—Case 14. D. F. Myxo-endothelioma.

FIG. 6.—Case 14. D. F. Myxo-endothelioma. General view of tumour structure. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

there is some tendency for fibrous tissue and fibrous processes to separate the individual cells.

In parts the tumour is very vascular, and capillary vessels are formed between the cells. Large vessels composed of a definite endothelial lining and fibrous tissue walls are very numerous. In some places there are groups of ten or more large vessels separated only by one or two layers of endothelial cells, or merely by the fibrous processes of these, and in some places there is considerable œdema surrounding the vessels.

The cyst wall appears microscopically to be poorly defined from the brain tissue, and its structure is very degenerate; many cells take practically no nuclear stain, and others contain blood pigment. The remainder of the substance is formed of cells of all shapes and sizes and thick fibrous bands. Everywhere the nuclei are pyknotic, and there is much granular debris. The appearance suggests that the cyst wall is formed from tumour tissue, rather than cerebellar tissue.

This is a somewhat unusual form of endothelioma, and quite unlike any other in the series. The appearances suggest a tendency to malignancy, and the apparent breaking down of the largest tumour, with the formation of small tumours elsewhere in the cerebellum, supports this view. The great vascular proliferation is also unusual. In all probability the seat of origin of the tumour was in the pia mater running between the lobules of the cerebellum (see figs. 1, 2 and 3).

### *Cylindroma.*

This name has been used by the German writers to describe a definite slow-growing form of tumour. They are usually met with in young subjects, most often in relation to the salivary glands, but they may occur elsewhere, and a considerable number of intracranial "cylindromata" have been described. Here we are dealing with a tumour which arises from a multipotential cell, which may be a germ cell (i.e., the tumour being a teratoma) or an undifferentiated mesoblastic cell (i.e., the tumour being a "terato-blastoma").

It is unnecessary to enter here into the discussion between these two theories of origin. In the present series these tumours have been provisionally labelled "myxo-endotheliomata," as the English school seems to favour their mesoblastic origin, and has not accepted the term "cylindroma" at all generally.

They consist of areas of myxomatous tissue surrounded and divided by bands of elongated cells covered with one or more layers of epithelioid cells which may be columnar or cubical in shape. In some of these tumours there are knots of cartilage, or of tissue which resembles cartilage but has not the consistency of fully formed cartilage.

The resemblance of the epithelioid cells to what is seen in some of the endotheliomata is sufficiently close to justify the inclusion of these mixed cell tumours in the mesoblastic group.

Both the cases in the present series were young children of 11 and 13 years, and in both the symptoms had lasted for some

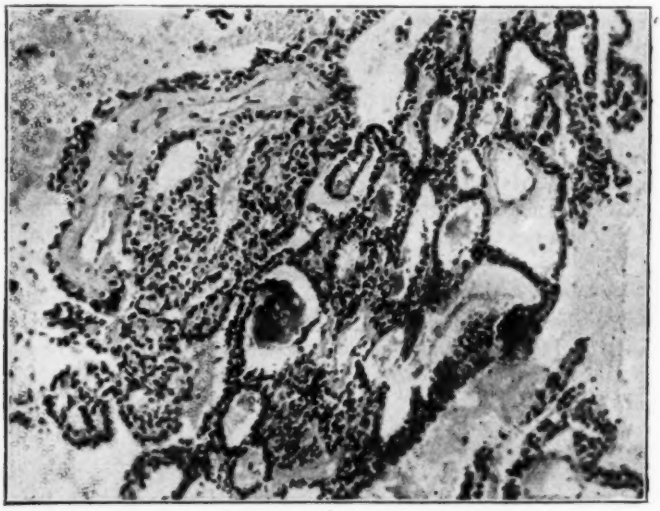

FIG. 7.—Case 15. E. E. Myxo-endothelioma. General view of tumour structure. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

years. In one case the tumour was at the base of the brain, and may have had some relation with the base of the skull, but in the other, where the growth was removed at operation, it was near the vertex of the cerebrum and appeared to have no connexion with the base. In both cases the tumour appeared to be a primary growth (see figs. 5, 6 and 7).

### "*Perivascular Sarcoma.*"

Macroscopically, it is a very difficult matter to distinguish endotheliomata from "perivascular sarcomata," but a careful examination of the surface of the tumour, as it shows on the cortex of the brain, may reveal, in the latter form, fine ridges which give exactly the appearance of a tightly packed bundle of fine white wool; whereas in the endotheliomata the surface is more granular. The line of separation from the brain

substance is very different; the endotheliomata peel out, leaving the brain tissue covered with a fine arachnoid layer, and are themselves covered with a similar layer; whereas the "perivascular sarcomata" are more intimately united with the brain substance, and bring away a small amount of brain matter attached to them.

The term "perivascular sarcoma" has been used provisionally for three tumours of this series. Their slow rate of growth, the macroscopic appearances of a rounded, granular or "woolly" tumour growing outwards from a central core, and the histological characteristics, especially with regard to the proliferative activity of the cells of the vessel walls, distinguish them from other sarcomata. It is not necessary to enter here into the controversy as to whether the tumour cells take origin from the adventitial endothelium, but there can be little doubt that the blood-vessels do play more than a subordinate part in their structure. It is to be noted that the classic type of "perithelioma" of von Hleb-Koszanska, occurring in the sacro-coccygeal region, has been called in question by Alezais and Peyron, who consider that the so-called "peritheliomata" of this region are in reality nerve-cell tumours, developed from remnants of the neural epithelium. It can be seen in the succeeding notes and illustrations how close the histological resemblances are between tumours classed as "perivascular sarcomata" and the "neuroblastomata."

The diagnosis of "perivascular sarcomata" from other forms of sarcomata lies in the appearances of the vessels, where the walls, formed of several layers of endothelial cells, seem to be everywhere budding out to form new vessels. In the older and more central parts of the growth the vessels are surrounded by several layers of fibrous tissue, and in places this has become hyaline; but towards the edges of the tumour and in the more rapidly growing forms this proliferative activity in the cells of the vessel walls is very well seen. In some of the tumours the cell multiplication is obviously rapid, and many irregular mitotic figures are seen in a dense cell mass. In others, the more characteristic arrangement of columns of cells surrounding in a irregularly radial manner a fairly thick-walled blood-vessel, suggests a slower growth, and the deficient vascularity is shown by the cell degeneration which takes place at a definite distance from the central blood-vessel.

Their relatively slow rate of growth is proved by one case in which five years elapsed between the onset of symptoms and death, whereas in the case which showed most histological evidence of malignancy symptoms appeared sixteen months before death. In all three cases the tumour was found in the substance of the brain, and in only one case did

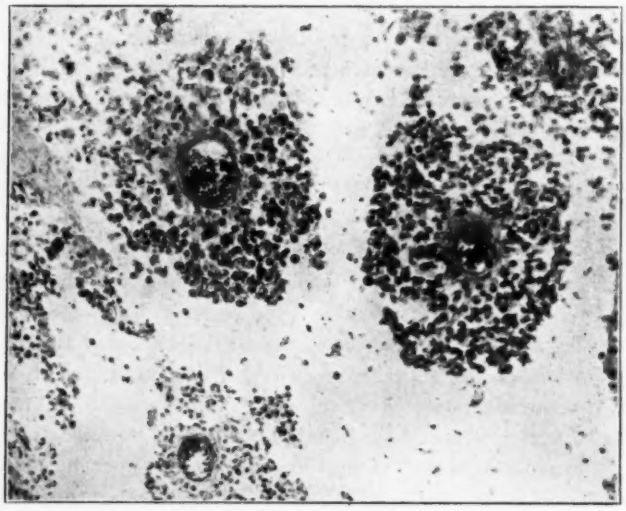

FIG. 8.—Case 16. P. M. "Perivascular sarcoma." The degenerated areas round columns of cells have fallen out of the section. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

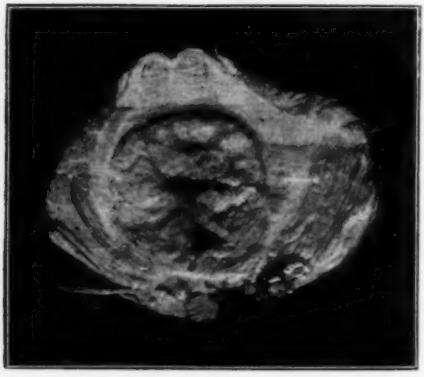

FIG. 9.—Case 17. S. S. "Perivascular sarcoma." Central tumour of cerebellum.

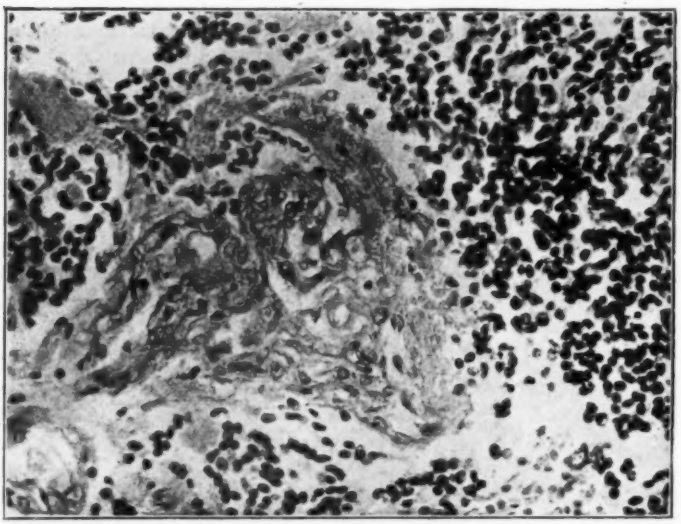

FIG. 10. Case 17. S. S. "Perivascular sarcoma." High-power view of small vessel. (Hæm. v. Gieson. Zeiss 8 mm. obj.)

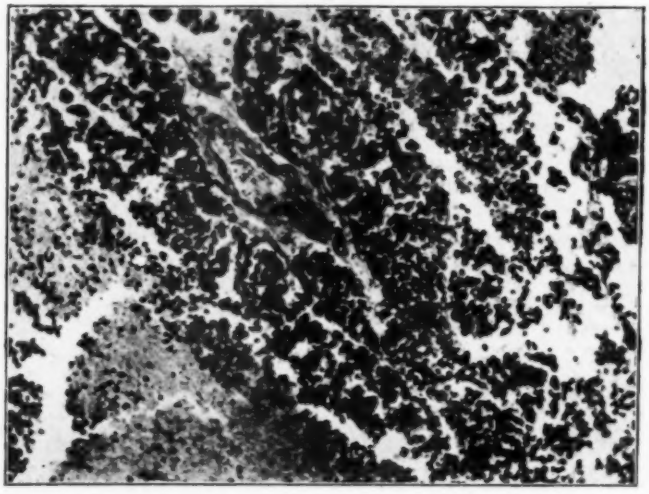

FIG. 11.—Case 18. C. P. "Perivascular sarcoma." Perivascular arrangement of cells with peripheral degeneration. Note cellular thickening of vessel walls. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

the tumour appear on the surface. In two, cystic spaces were formed in the tumour, whereas in the third a depressed area of softening was seen on section.

It may be that later work will class many forms of this type of tumour under tumours of nervous origin. They undoubtedly show much in common with the neuroblastomata, and with certain tumours (e.g., Case 30) which have been classed in the past either as sarcomata or gliomata (see figs. 8 to 11).

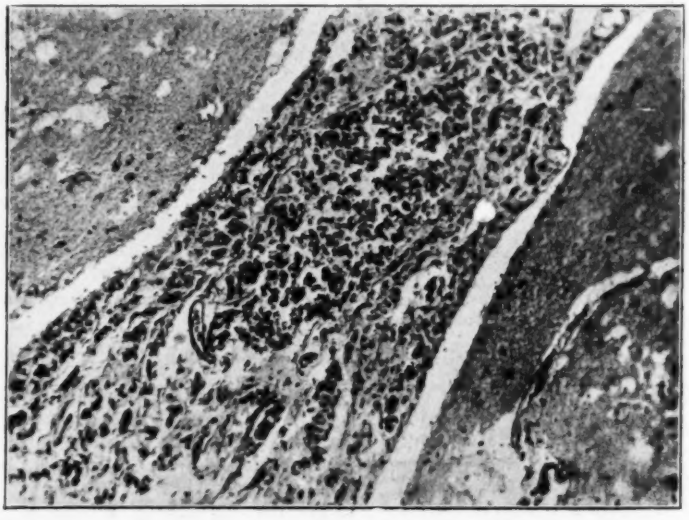

FIG. 12.—Case 19. W. P. "Sarcomatosis of meninges." Sulcus on cortex of brain, showing infiltration of arachnoid with epithelioid cells. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

The following anomalous case has provisionally been classed as "*sarcomatosis of meninges.*"

*Case* 19.—W. P. (physician, Dr. Wilson). Admitted May 1, 1916; died July 3, 1916.

*History.*—Headaches began in January, 1916, along with an attack of vomiting and followed by occasional loss of power in the right leg. A decompression operation was performed after admission on the left side of the skull, but no tumour was found.

*Macroscopic appearances.*—There is a large hernia on the left side of the brain, a considerable degree of hydrocephalus was present, and there was a definite thickening of the membranes round the fourth ventricle. The pia mater was thickened in the sulci and to a less extent over the convolutions, and round the pons and the cisterna magna it is greatly thickened up to 2 mm.

On section of the brain the ependyma appears thickened and strips off as a membrane about 1·5 mm. thick. (This is partly due to faulty preservation.)

*Microscopically*, the meshes of the arachnoid, both over the base of brain and the sulci of the cortex, are densely packed with small rounded cells. These have a granular cytoplasm and a rounded nucleus, which is usually placed somewhat eccentrically. The cells tend to group themselves into irregular bunches or columns, and are more closely packed in some places than in others. They fill up the adventitial lymph spaces of the blood-vessels in the arachnoid. They are separated from the cortex of the brain by pia mater, through which they show no tendency to pass. Blood-vessels running in from the pia mater, however, in many places contain numerous cells in their adventitial sheaths, and the vessels which run into the optic thalamus from the base of the brain are surrounded by a thick sheath of similar cells. The optic nerves are also surrounded by a sheath of cells of similar character.

The hydrocephalus is apparently due to blockage of the foramina of Majendie and Luschka, and the general damming back of the subarachnoid circulation.

The nature of the cells which fill the spaces of the arachnoid is by no means clear. At first sight their close resemblance to the cells lining the ventricles suggested that they might be of the nature of a desquamation of the ependymal cells. But there is no evidence of disease or desquamation of this membrane. On the other hand, the arrangement of the cells in the meshes of the arachnoid suggested some more definite tumour formation. The "acinous" arrangement may be purely due to the meshes of the arachnoid membrane, but it does suggest that the cells are actually multiplying in these meshes. And it is doubtful whether such a widespread and regular involvement of the membranes all over the cortex as well as the base could possibly occur purely as a result of the carriage of cells by the cerebrospinal fluid. A possible explanation is that the cells filling the arachnoid arise as a neoplastic overgrowth of the endothelial cells lining the arachnoid meshes, and that this is a form of endothelioma.

It seems likely that cases of this kind have previously been described under the heading of "Sarcomatosis of the Meninges" (see fig. 12).

## Tumours of Nervous Tissue.

With regard to the typical gliomata little need be said. Their diagnosis rests as much with the macroscopic as with the microscopic appearances. For, as Bruns points out, a greyish gelatinous tumour infiltrating the brain substance, but causing little alteration of its appearance, is almost certainly a glioma. There may be smaller or larger areas of hæmorrhage or softening with the formation of cysts, and at times it may be difficult to distinguish such appearances from those of purely vascular disease. In such cases the history may be a help, but the

FIG. 13.—Case 20. A. B. Glioma. Hæmorrhagic glioma filling up third ventricle, causing hydrocephalus of lateral ventricles.

FIG. 14.—Case 21. W. W. Glioma. Softening in gliomatous area of right centrum ovale communicating with the surface by a narrow channel, and simulating a wound of the brain.

diagnosis rests in the end with the microscope. Such difficulties were presented by Cases 20 and 21, where on clinical grounds the diagnosis of tumour was made, but the macroscopic appearances threw doubt on this, until the diagnosis was confirmed by examination of microscopic sections (see figs. 13 and 14).

In many cases where the undifferentiated character of the tumour cells causes a diagnosis of sarcoma to be made, it may be noted that the blood-vessels have a thicker endothelial lining than is usually seen in "small round-celled sarcomata," and that the cells are not in reality round cells, but are stellate, their angles being prolonged into fine processes which can be traced for some distance. A confirmation of the diagnosis may sometimes be obtained from the fact that, when multiple, the growths remain limited to the nervous system (see Case 30).

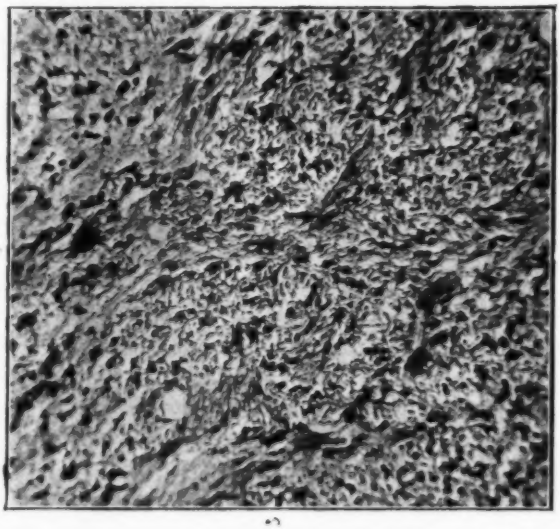

FIG. 15.—Case 26. T. W. Glioma. A glioma of a rather fibrous type. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

For the most part the cells of a glioma resemble the "spider" cells of tissue reaction in the central nervous system, but tend to have a more clearly defined ring of cytoplasm than the mature spider cell. In some tumours they are elongated and resemble fibroblasts, but sections stained with iron-alum hæmotoxylin show that the terminal processes are not single fibres, but break up immediately on leaving the cell

body into two or more stems, which may again branch before they join with similar processes from neighbouring cells (see fig. 15).

The blood-vessels have always a definite endothelial lining, but this has usually little or no fibrous tissue support, and as in some places vessels of this type attain a considerable size, it is natural that the walls should sometimes give way and hæmorrhages of larger or smaller size occur. The amount of vascularity varies very considerably, both in different tumours and in different parts of the same tumour; and in the less vascular parts ischæmic degeneration and softening often occur.

Case 27, R. H., presents a common enough picture of multiple gliomata of the brain-stem and cord. As is usual in gliomata of the cord these tumours are more or less rounded, but blend insidiously with the surrounding nerve tissue. They are rather more vascular and of a greyish colour (especially after fixation) than the surrounding white matter, and hæmorrhages into their substance are common.

The *small sub-ependymal tumour in Case* 28, *X. Y.* (fig. 16), is not very easy to classify. Its position and histology seem to relate it to the cells of the ependyma, but it differs from true "ependymomata" in that the columnar cells, though blending with glial tissue at one end, are not free at the other end as in ependyma and in the lining membrane of the central canal of the cord, but are prolonged into long, fine fibrils which run towards the centre of the column where they appear to join with similar processes from surrounding cells. This arrangement is similar to that described in some of the "neuroblastomata" (though none in the present series show it), and to the so-called "rosette" arrangement in gliomata of the retina, where, however, the cells are more rounded. In Case 28 the cells are clearly of ependymal type, and the difference of structure refers back to an earlier period in the development of these cells, when the "spongioblast" cell has a definite process at either end. The loss of one process, or its metaplasia into ciliæ, takes place with the more mature development of the cells and their more definite arrangement around the cavities of the brain and cord.

The term "spongioblastoma" used by Ribbert and other writers for tumours of this nature has much to commend it, and is less cumbersome than the older term of Rosenthal, "neuro-epithelioma gliomatosum." The term "ependymoma" usually refers to a tumour where the cells are arranged round cavities as are ependymal cells, and is thus less generally applicable. They are usually rounded, clearly defined tumours, either situated close to or in the ventricles of the brain or in the centre

of the cord. The association in Case 28 of a tumour of this kind with a glioma in the opposite hemisphere of the brain is of extreme interest and is suggestive of their common origin.

Areas of "spongioblasts" occur in many tumours of nervous origin which resemble gliomata or neuroblastomata in their general characteristics. And their similarity in appearance and probably in origin also to the rosettes seen in gliomata of the retina has already been noted. It is suggested that the term "spongioblastoma" should not be applied to such tumours, but reserved for tumours where the whole structure, as in the present instance, or the majority of the tissue, consists of columns of spongioblastic cells. The presence of spongioblasts suggests that the tumour arises from some "cell rest" which was isolated at an early stage of development when glia cells had just begun to be differentiated from spongioblastic cells, and the resulting tumour tends to reproduce both types of cell.

*Case* 28.—X. Y. (Dr. Batten).

*Microscopic appearances of the small, round subependymal tumour, lying close to the left lateral ventricle.* The characteristic portions of this tumour show rounded or irregular columns, composed of an outer zone of nuclei in several layers, and a core which resembles the ground substance of brain tissue, staining brownish with van Gieson's stain. Some of these columns are cut transversely, others more longitudinally, but they are obviously very irregular in shape and branch in all directions. In some of them there is a number of cells lying in the core, but, on the whole, it is devoid of nuclei. In sections stained with iron-alum hæmatoxylin, the cells forming the outer zone are seen to be mainly elongated cells, with a long process running into the core and merging insensibly with the processes of other similar cells, and at the outer end one or more short processes, finer and less easily traced, which seem to blend with processes of the cells which lie between these columns. In addition, there are in this zone a number of binuclear and polynuclear cells of rather more rounded outline and less definite processes. In between the columns the tissue is very cellular, the cells being of very varying size and shape, mainly with a single rounded or oval nucleus and ill-defined processes, but many very large polynuclear cells are also seen, some with a ring of nuclei at the periphery and a clear centre, others with the nuclei more centrally placed. These cells are more globular in shape than the mononuclear cells, but have several short processes which join with the processes of surrounding cells.

The blood-vessels run in the tissue between the columns, and are nowhere seen in their substance. They are composed of a single layer of fibrous tissue and an endothelial lining.

The tumour is obviously of the glial type, the cells which lie between the columns being exactly those seen in a typical glioma, and the cells forming

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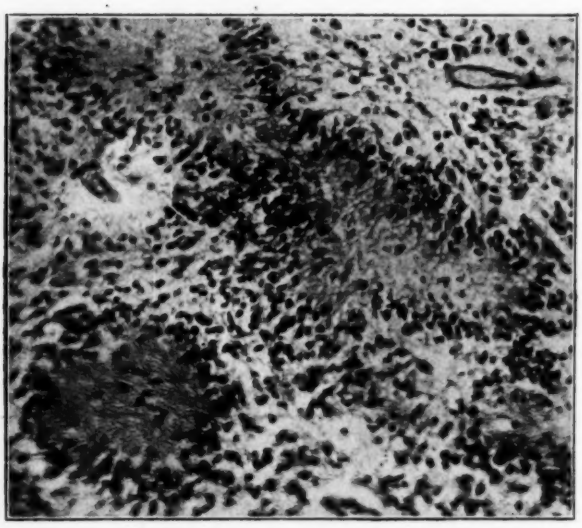

FIG. 16.—Case 28. X. Y. "Spongioblastoma." Spongioblast tumour. Note that the vessels run in glial stroma outside the columns of spongioblast cells. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

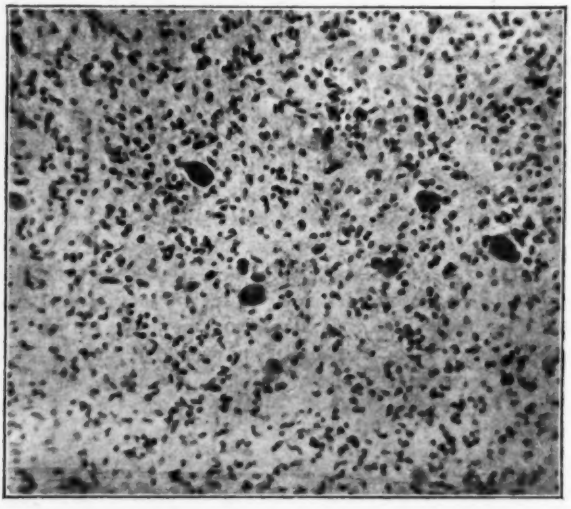

FIG. 17.—Case 29. L. R. Glioma pontis. The nerve-cells in the infiltrated area are undergoing degenerative changes, but one is practically normal. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

the columns being similar to the ependymal cells surrounding the central canal, with the difference that the longer process runs inwards instead of outwards as it does in the central canal.

Except for the fact that the ventricular ependyma is seen to run over the tumour with very little alteration, it might have been supposed that the tumour was formed by villous protrusions of the ependyma (so to speak); although in that case the blood-vessels and gliomatous tissue would have been inside and not around the columns.

Both the situation and the nature of the tumour suggest that it is a neoplasm of the ependymal cells, a so-called "spongioblastoma" (see fig. 16).

Case 29 presents a very typical example of the condition which used to be described as "hypertrophy of the pons."

*Case* 29.—L. R., aged 24 (physicians, Drs. Hinds Howell and Saunders). Admitted January 7, 1918. Died August 6, 1918.

*History.*—Patient was flying on August 18, 1917, and was obliged to make a "forced landing," falling twenty feet. He was unconscious after this for one and a half hours. He recovered sufficiently to go on duty again that day, but two days later his right ankle "did not go right"; on the third day he had a bad attack of "colic," and could not speak or chew properly. He became progressively worse; on admission he had right hemiplegia.

*Macroscopic examination.*—The chief obvious abnormality of the brain, as seen from the base, is enormous enlargement of the pons, chiefly of the left side. A horn-like outgrowth is seen near the upper border of the left side of the pons, and a similar but smaller growth on the right side.

On section, except for the enlargement, very little abnormality is seen, the transverse striations being well marked, but there is a small area of softening about the centre of the pons under the floor of the fourth ventricle.

The enlargement extends from the pons up into the mid-brain and crura cerebri, and downwards into the medulla.

The transverse diameter at the upper end of the pons is 6·5 cm.: anteroposteriorly the greatest width at this level is 5 cm.; the length of the pons, from mid-brain to medulla, is 3·5 cm. At its junction with the cerebrum the mid-brain measures 4 cm. in transverse diameter, and 4·5 cm. in anteroposterior diameter.

*Microscopic examination.*—Sections of the pons show a fairly loose texture of glial cells of all kinds, most of them with well-defined processes, corresponding to the elongated spider cells of glial reaction. Many are multinucleated, some globular and of large size, and cells with rings of nuclei around their periphery are fairly common. The nerve-cells in the area infiltrated by the tumour show some degeneration, the bodies being more globular than normal, the nuclei rather hyaline, and in some cases eccentric, and the cytoplasm containing large numbers of brownish granules. No "neuronophagy" is seen, however. (See fig. 17.)

The blood-vessels are numerous and well formed, even the smallest having

a definite ring of endothelial cells. Some show considerable proliferation of the cells of their adventitial coats, as well as infiltration of the adventitial lymphatics. The latter is especially seen around the area of softening under the floor of the fourth ventricle. In the actual area of softening, only the outline of the vessels and cells can be seen, with no nuclear staining. The blood-vessels in the immediate vicinity are all distended, and their adventitial spaces packed with cells.

### *Multiple Gliomata of the Nerve-roots.*

This rare condition is illustrated by the following case :—

*Case* 30.—L. S. (Dr. Collier), aged 13. Admitted April 11, 1918. Died, May 26, 1918.

*History.*—Vomitings commenced two months before admission, followed a fortnight later by headaches, and a burning pain over his eyes. He also had diplopia, and pain in the legs. On April 24, 1918, a subtentorial decompression operation was performed, but no tumour was found.

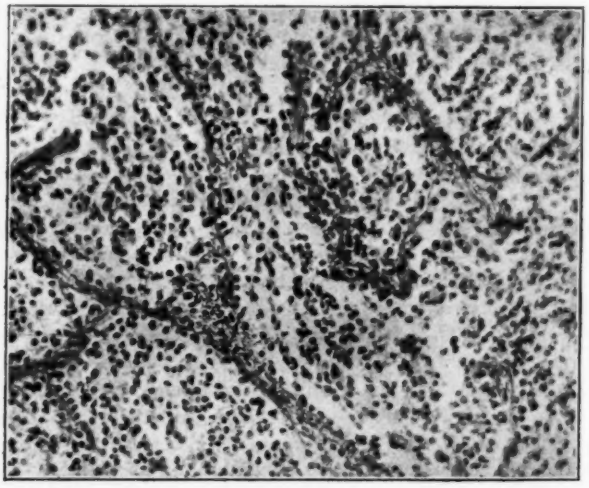

FIG. 18.—Case 30. L. C. "Multiple gliomata of nerve-roots." General view showing arrangement of cells along the walls of vessels. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

*Macroscopic appearances.*—At the post-mortem examination a number of small tumours were found, as follows :—

(1) There is a fleshy, flattened tumour replacing the left olfactory bulb, and slightly adherent to the membranes covering the cribriform plate.

(2) Between the crura cerebri, filling up the sulcus oculomotorius, is a round tumour mass about 1 cm. in diameter, reaching up to within 2 mm. of the floor of the third ventricle.

(3) At the centre of the pons there is a large mass which fills up the ponto-cerebellar angle on both sides. It is larger on the left side than the right, and in size and shape is like a broad bean.

(4) On the left side of the upper part of the medulla is a large mass, pressing inwards from the groove between the medulla and cerebellum to 3 mm. from the middle line, and measuring 15 mm. transversely and 10 mm. antero-posteriorly.

(5) There is a very small tumour at the same site on the opposite side 3 mm. in diameter.

The cord is covered both anteriorly and posteriorly with fleshy sessile growths, varying in size. At the mid-dorsal level (seventh dorsal) they compress the cord on either side so that it is narrowed to the width of 4 mm. There is scarcely a nerve-root which has not one of these sessile growths attached to it.

*Microscopically*, these tumours resemble one another in every particular. They are composed of small cells with rounded nuclei of much the same size, and relatively little cytoplasm, which usually forms a fine ring round the nucleus, but sometimes is in the form of one, two or more processes which blend with the processes of other cells. All the cells are irregular in shape, their angles being prolonged into fine fibres which form a fine reticulum in all parts of the tumour. Some of the cells have two or more rounded nuclei, and some are rather larger than the majority and resemble very closely the medium-sized glia cells of normal glial reaction.

The arrangement of the cells is to some extent perivascular, as each vessel is outlined by a fairly definite sheath of cells which seem to be attached to its wall. From this they spread out in broad fern-like clusters, so that in the thicker parts of the growth no interval is seen between the cells surrounding different blood-vessels.

In paraffin sections cut at six microns, the cells are fairly closely packed, but not so close as in lymphoid tissue, which thicker celloidin sections resemble to some extent; the interval between the cells is at least as wide as the cell body. Arrangement in small rosettes is seen in some parts of the growths, but is not so common as to be a characteristic feature.

The blood-vessels are of fairly large size with well-formed fibrous tissue walls and a thin endothelial lining; and they are obviously in process of forming new channels, as small buds can be seen to spring from the older vessels all along their course. In sections which cut a vessel transversely there are usually to be seen small, almost capillary channels in the adventitia, and sometimes as many as four or five channels of approximately equal size are seen running together. This appearance is similar to that seen in Case 17, but is even more marked.

The tumours do not tend to invade the substance of the brain or cord but are separated from it by a thin layer of pia mater. Nor do they infiltrate the nerves after these leave the tumour (see fig. 18).

Case 30 presents a condition which, I can only suppose, is a transition

between multiple gliomata and multiple neurofibromata of the central nervous system (see Case 35, N.R.S.). In this case one olfactory bulb, and almost every nerve-root from the third cranial pair to the cauda equina, was the seat of a small nodular tumour of greyish gelatinous appearance, which consisted histologically of a mass of small cells with rounded nuclei grouped around vessels. The points in favour of this being a type of glioma are:—

(1) The cells are stellate, the angles being prolonged into fine processes as seen especially well by Alzheimer's "fuchsin and light-green" method.

(2) The vessels are well formed as far as their endothelial coat is concerned.

(3) All tumours have the same relation to the central nervous system, i.e., they arise at the junction of the peripheral nerves with the central nervous system.

It is to be noted that the optic nerves have no tumour arising from them, as they are developmentally outgrowths from the central nervous system, and not properly speaking nerves. The anterior part of the olfactory bulb receives the filaments of the olfactory nerve, and so stands in the same category as, say, the junction of the eighth nerve with the pons. No tumours were found in the substance of the brain or cord, nor elsewhere in the body, so that the presumption is that we are dealing here with a congenital condition of unstable equilibrium in the transition zone between the glia and the sheath of Schwann.

The theory might be advanced that the tumours are secondary to a primary growth, say at the junction of the sixth pair with the pons, and that their site is due to tumour cells being carried by the cerebrospinal fluid, but in that case one would expect to find tumours growing in the sulci of the brain and round the base rather than attached to nerve-roots. And if the tumours were of connective tissue origin they would surely have found their way to other parts of the body, or would at least have invaded neighbouring mesoblastic tissues.

### *Neuroblastoma.*

This term is coming into common use to designate a fairly large group of tumours of varying malignancy, which are characterized by the formation of nerve cells and nerve fibres. It is questionable whether it should be restricted to those forms which recall the earliest stages of differentiation of the neuroblast, or if it should also include the typical "benign ganglio-neuroma," in which both cells and fibres

are identical with those of a spinal root ganglion. All these tumours are most commonly found in relation to the sympathetic nervous system, or the suprarenal body, and Alezais and Peyron divide those occurring in such situations into three classes: (1) "Sympatho-gonioma" composed of cells resembling the undifferentiated neuroblasts; (2) "parasympathoma," in which the cells tend to the chromaffin type of the medulla of the suprarenal, the carotid gland, &c.; and (3) the "sympathoblastoma" (ganglioma embryonale sympatheticum of Pick) or "ganglioneuroma of the sympathetic" in which the cells and fibres reproduce those of the nervous system.

Similar tumours occur in the brain and cord, either as the fully differentiated or more embryonic type, but descriptions of these are very rare, and the tumours are usually situated in relation to the ependyma of the ventricles. Homer Wright records one of the cerebellum among several of the sympathetic system.

In the present series four tumours have been included under the neuroblastomata, three of which were tumours of the centrum ovale, and one was in relation to the hypophysis. The last named differed from the other three in approximating much more closely to the classical type of ganglio-neuroma, but it gave evidence of being less fully differentiated, and having more tendency to malignancy than the typical "ganglioneuroma." It is very possible that it arose from the "pars nervosa" of the pituitary, as the symptoms (hyperpituitarism followed by adiposity) pointed directly to altered function of the hypophysial gland. The relationship of this part to the medulla of the suprarenal is very close, although their autacoids are certainly distinct, and on this analogy it would not seem unlikely that undifferentiated nerve cells present in the pars nervosa might give rise to a similar tumour to that arising from suprarenal medulla.

### *Neuroblastoma (Malignant).*

*Case* 31.—W. H., aged 26 (physician, Dr. Collier). Admitted January 21, 1918. Died February 21, 1918.

*History.*—Six weeks before admission he had a pain in the back of the head which came on at night. He only vomited when he got out of bed. On admission he had weakness of the right arm, bad sight and diplopia. January 20, 1917: Left parietal decompression operation, no tumour seen.

*Macroscopic appearances.*—A very large tumour was found in the anterior part of the left hemisphere, spreading from the dura, and occupying the whole frontal lobe with the exception of a layer about 1 mm. wide on its anterior and inner surfaces.

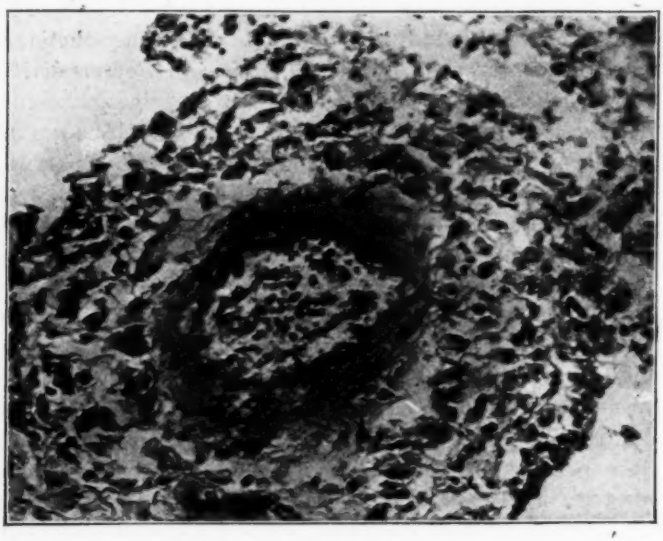

FIG. 19.—Case 31. W. H. Neuroblastoma. A similar arrangement round vessels is seen in this case to that in Cases 32 and 33. (Bielschowsky's method. Zeiss 8 mm. obj.)

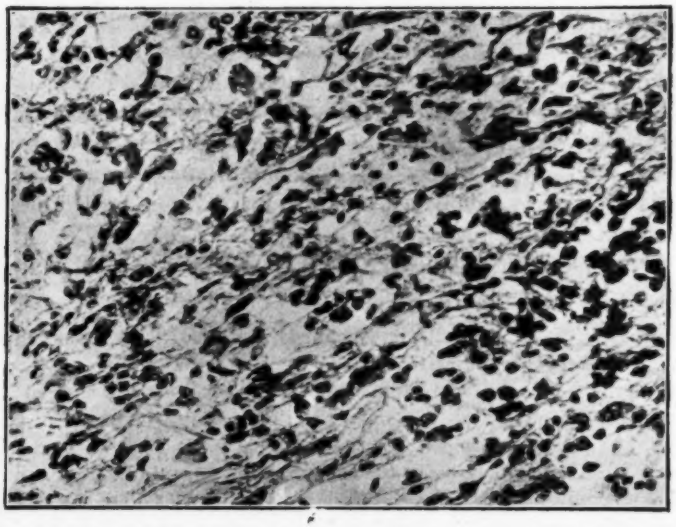

FIG. 20.—Case 31. W. H. Neuroblastoma. Gliomatous area, but with rather thicker and better defined fibres running from the cells than in gliomata. Compare with fig. 15. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

The cortex of the temporal lobe is invaded, and the tumour is adherent to the dura mater over an area of about 3 mm. anteriorly.

On section it presents a very irregular appearance, with splashes of yellow and black (after formalin fixation). It is granular on the surface and fairly well defined from the brain tissue, though on attempting separation it leaves a granular deposit behind. It is apparently separated from the brain tissue in places by a thin layer of arachnoid tissue.

Microscopically this is a very cellular tumour, composed of a great variety of cells, and with a great number of giant cells, either multinucleated or with ring nuclei around their periphery. The latter are mostly grouped together in the neighbourhood of large vessels. Many of them are globoid in shape, others fusiform or pear-shaped with long processes; some show mitotic figures. Smaller multinucleated cells are scattered all through the tumour, but the great majority of the cells present are small cells with small nuclei and relatively abundant cytoplasm, running off into shorter or longer fine processes. In the parts of the tumour neighbouring on the brain tissue, areas of necrosis are very plentiful; in these the nuclei are pyknotic or granular and indefinite.

Large blood-vessels are very numerous, many of them surrounded by small round cells resembling lymphocytes, but with rather more cytoplasm. Plasma cells are not seen. Of the smaller vessels some have fairly definite walls, but capillary vessels are very scanty, those present being in the peripheral parts of the tumour, and being probably the blood-vessels of the original nervous tissue.

In sections stained by Bielschowsky's method, no nerve fibres can be seen, but faintly staining fibres of varying thickness are plentiful. The large cells do not show any special staining by this method, and their processes are only faintly stained (see figs. 19 and 20).

By Weigert-Pal staining no myelinated nerve sheaths can be found, at least in the more central parts of the tumour.

### *Neuroblastoma.*

Case 32.—T. H., aged 35 (physician, Dr. Farquhar Buzzard). Admitted, April 5, 1917. Died, August 29, 1917.

*History.*—In March, 1911, the patient fell down and was unconscious for a quarter of an hour, but was able to walk home later. Two days later he had another attack, followed by severe occipital headache. After this he had good health until December, 1912, when he had another seizure accompanied by headache. Since that time the headache had been constant. In October, 1915, his sight began to fail, and since Christmas, 1916, he had been quite blind.

In July, 1916, he lost the sense of smell, and in October, 1916, his gait became unsteady. Optic atrophy was present at the date of admission to hospital.

Operation, April 26, 1917. The first stage of a subtentorial decompression was performed, and this was completed on July 20, 1917.

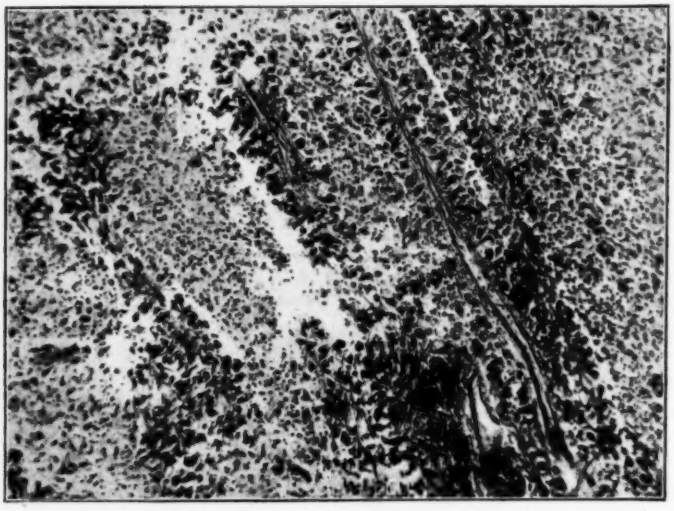

FIG. 21.--Case 32. T. H. Neuroblastoma. A general view of the perivascular grouping of large pyriform cells. (Heidenhain's hæm. Zeiss 16 mm. obj.)

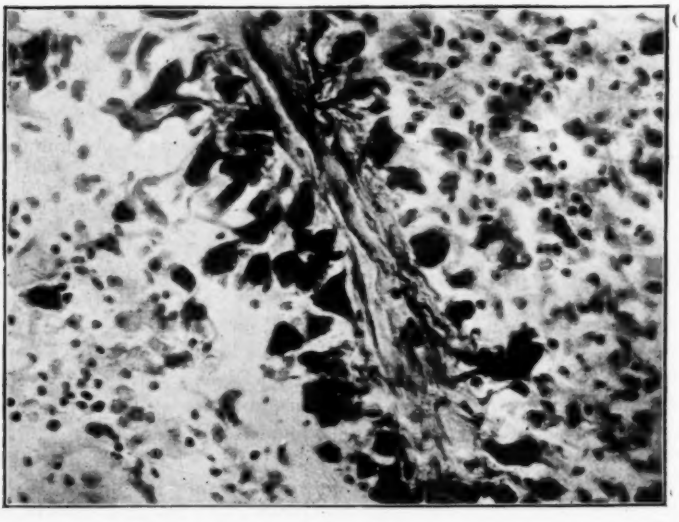

FIG. 22.—Case 32. T. H. Neuroblastoma. High-power view of same area. The large (? nerve) cells are seen ringing a small vessel with whose walls their processes join. (Heidenhain's hæm. Zeiss 8 mm. obj.)

*Macroscopic appearances.*—A small sub-cortical tumour is present extending to the posterior horn of the lateral ventricle, and lying under the cortex in the posterior part of the temporal lobe; the tumour is rounded in outline but not clearly delimited from brain substance. It measures in sagittal diameter 4·5 cm., in coronal 2·5 cm.

*Microscopically* the tumour is composed of cells of the glial type which are for the most part fairly large, globular or fusiform, with a considerable tendency to glial fibre formation, more in some parts than in others. In some places there is a fairly thick felt work of glial fibres, with relatively few glial cells; in other parts there are collections of large fusiform cells, which surround a blood-vessel in a single or double ring, being attached to its walls by one or two processes and sending out other processes into the surrounding tissue. In some parts of the tumour most of the blood-vessels are outlined by rings of such cells (see figs. 21 and 22).

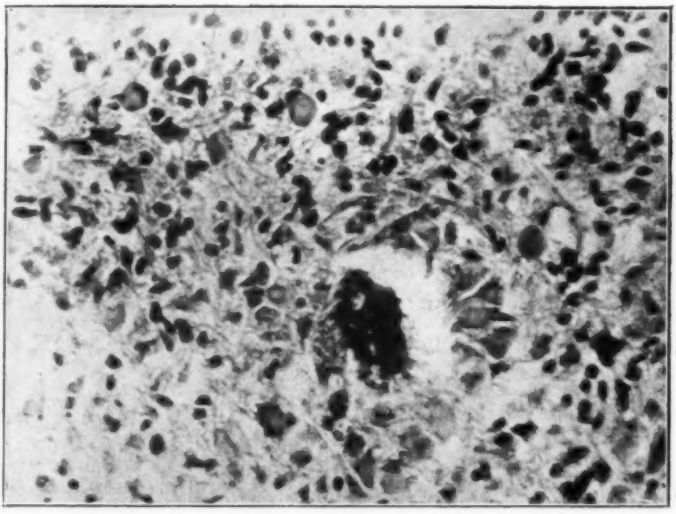

FIG. 23.—Case 32. T. H. Neuroblastoma. Showing arrangement of large cells round vessels. No darkly staining nerve-fibres are seen. Compare with figs. 19 and 22. (Bielschowsky's method. Zeiss 8 mm. obj.)

Elsewhere in the tumour the cells are irregular in size and shape, with a tendency to have more than one nucleus. The neighbouring brain tissue is compressed as is shown by concentric lines of glial tissue, and there is a definite zone of division between brain matter and tumour formed of these lines. In the tumour tissue, both in the lymph spaces and lying free in the tissue between the collections of large cells described above, there are aggregations of cells resembling compound granular corpuscles.

In some parts of the tumour there are areas of cells and fibres which closely resemble the structure of a posterior root ganglion. Giant cells measuring 30 microns or more, either of glial or nerve cell type, with one or more nuclei, are present in places.

By Bielschowsky's staining method (see fig. 23) a few axis cylinders are present in most parts of the tumour, but they seem to be most numerous in those parts which are composed chiefly of smaller types of cell. In the neighbourhood of the large globoid and fusiform cells they are not numerous if we count only those which stain a deep black, but there are numerous fibres, some thick, others finer, which stain greyish with the silver and which can be seen to arise from the large cells. It was impossible to trace any fibre for a distance from its parent cell, or it is possible that a similar connection might have been established between these paler staining fibres and the darkly stained fibres, to that which it was possible to trace in Case 34; but the way in which the processes of the large cells stained with Heidenhain's hæmatoxylin, i.e., very much more darkly than any glial fibres, suggests that they are more closely related to nerve than to glial fibres. By the Weigert-Pal method some fine myelinated sheaths are to be seen in the peripheral parts of the tumour, but no fibres are present in the more central parts. Those present seem either to have been left behind or regenerated around partially damaged axis cylinders.

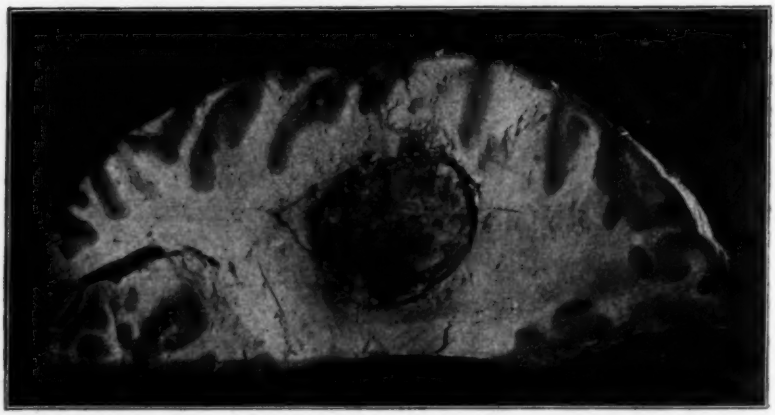

FIG. 24.—Case 33. Pte. E. Neuroblastoma. Horizontal section through the tumour.

### *Neuroblastoma (Malignant.)*

*Case* 33.—Private E. (physician, Dr. Taylor). Admitted December 5, 1916. Died January 15, 1917.

*History.*—Six weeks before admission the patient had a septic thumb resulting from a cut. He was in bed for a week with this. Two weeks later the thumb became worse and he at that time lost the use of the arm and leg

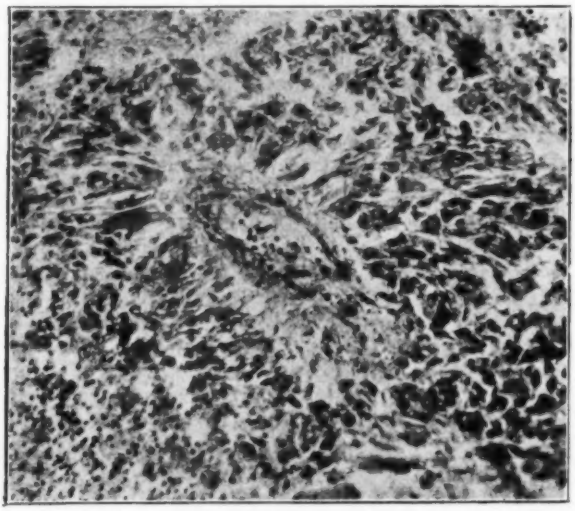

FIG. 25.—Case 33. Pte. E. Neuroblastoma. General view of the arrangement of the large cells round a vessel, with degenerated areas more distally. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

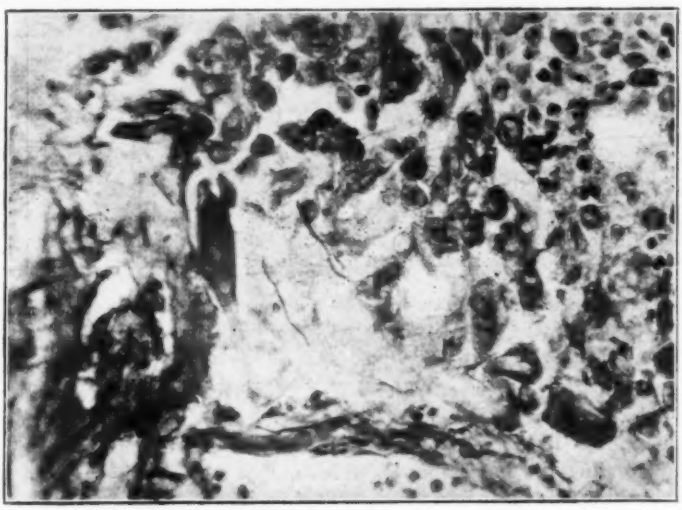

FIG. 26.—Case 33. Pte. E. Neuroblastoma. Field showing numerous nerve-fibres and wall of vessel to which a large (? nerve) cell is attached by a firm process. (Bielschowsky's method. Zeiss 8 mm. obj.)

on the same (the right) side. He also had aphasia. On admission he had optic neuritis. He had no vomiting.

*Macroscopically*, the dura was noted at the post-mortem to be adherent to the skull over the left motor area. On section of the brain there was found to be a well-defined granular, greyish tumour in the left centrum ovale, 2 cm. from the cortex of the parietal lobe and 2·5 cm. from the mid-line. It extends for 5 cm. in sagittal and 3 cm. in transverse diameter. In appearance it is fairly well defined from the brain substance, especially in the outer part. There is a thin friable capsule, and, when shelled out, brain tissue remains adherent to it. Blood-vessels enter by a hilum on its inner surface. There are some hæmorrhages into the substance in this region, and a moderate degree of dilatation of the ventricles is present on the side opposite to the tumour (see fig. 24).

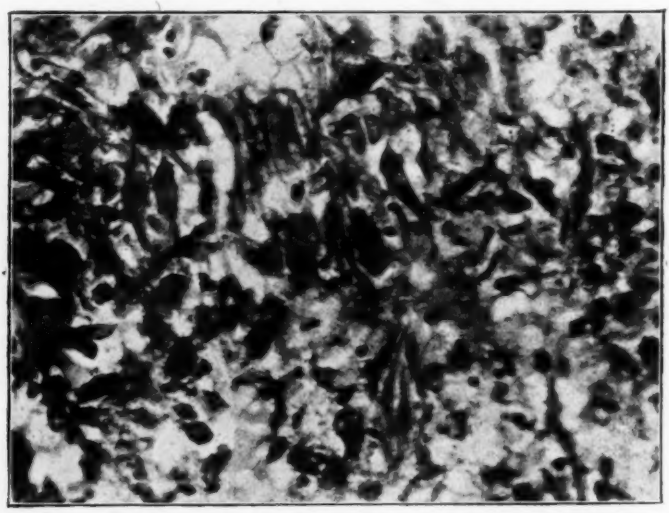

FIG. 27.—Case 33. Pte. E. Neuroblastoma. A number of nerve-cells are shown, and a few twisted nerve-fibres. (Bielschowsky's method. Zeiss 8 mm. obj.)

*Microscopically* there is considerable difficulty in finding a portion of the tumour which is not too degenerated for the structure to be recognized; but everywhere, even in the most degenerate parts, there are small collections of cells surrounding the blood-vessels, which are of medium size and supported by a fairly thick ring of fibrous tissue. These cells are of all shapes and sizes, but among them is a large proportion of giant cells with one or, more commonly, several nuclei. These have long thick processes, which can be traced for some distance; usually one of these is longer and thicker than the others. Many

of these processes are attached to the vessel walls, but this arrangement is not so definite or so frequently seen as in Case 32 (see fig. 25).

In addition to these large cells there are everywhere smaller cells, both plasma cells and polymorphonuclear cells being plentiful, especially in the neighbourhood of degenerated areas, but small rounded cells which it is impossible to classify are also numerous. In sections stained by Bielschowsky's method very numerous axis cylinder and other nerve fibre processes are seen, some of which can be seen to arise from the large cells. These processes are all very contorted and irregular, and in places swellings which suggest "Boules terminales" can be made out. The character of these processes and their presence in the central parts of a tumour which shows such great degenerative changes, makes it almost certain that they are derived from the tumour cells (see figs. 26 and 27).

By Nissl staining it is impossible to say that there are any granules in the cells, but some cells stain more irregularly and patchily than others.

There is no evidence of glial cells or fibres in the more central parts of the tumour, but between it and the healthy brain tissue there is a fairly wide zone of thickly felted glial tissue with numerous cells, which resembles very closely the structure of a glioma. It is through this zone that the tumour shelled out. No myelinated fibres could be found by the Kultschitsky-Pal method (see figs. 23-26).

### *Neuroblastoma or Ganglioneuroma.*

*Case* 34.—M. B., aged 26 (physician, Dr. Stewart). Admitted August 9, 1917. Discharged I.S.Q., October 11, 1917. Readmitted June 10, 1918. Died June 27, 1918.

*History.*—Headaches started after the birth of a baby, two and a half years before admission, and were very severe, especially behind the right eye. Her sight deteriorated from that time onwards.

On admission she was seen to be a case of acromegaly, with the typical enlargement of cranium, tongue, hands and feet, and underhung lower jaw, so that the teeth could not come together; she also had brown pigmentation of both axillæ and on the skin of the abdomen.

*Macroscopic appearances.*—The whole base of the brain is covered with a nodular tumour mass, the nodules being more or less distinct from one another, but joined by their capsules. The whole mass reaches from the olfactory bulbs to the antero-inferior surface of the pons.

Over the region of the olfactory bulbs the tumour has to some extent been removed (by operation). Posterior to this the tumour mass is diffusely stained with hæmorrhages, and extends antero-posteriorly for 9 cm., laterally for 5 cm.; vertically the greatest measurement is 4·5 cm. (see figs. 28 and 29).

Of individual tumour nodules the largest measures 3 cm. in diameter, the smallest 7 mm. They do not infiltrate the brain at any part, being attached loosely to the meninges.

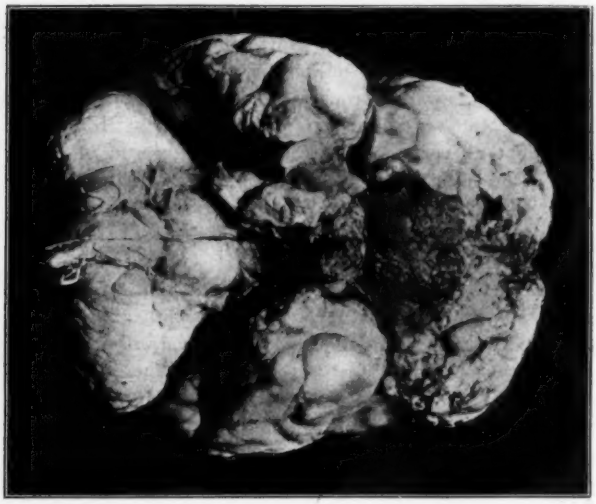

FIG. 28.—Case 34. Mrs. B. Ganglioneuroma. View of tumour from the base. The posterior part of the tumour on the left side of the mid-line has been removed for histological examination.

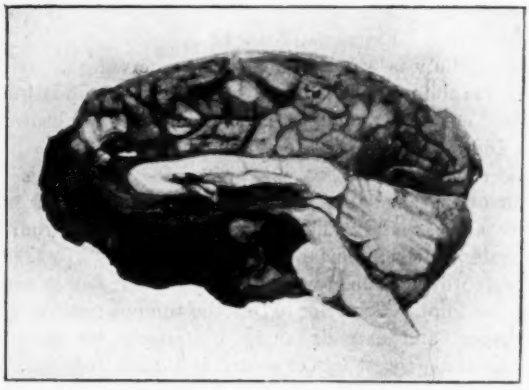

FIG. 29.—Case 34. Mrs. B. Ganglioneuroma. View of section between hemispheres of brain. The dark blood-stained area anteriorly is due to exploratory operation.

No trace of the pituitary body can be found. The tumours are pressed more into the right frontal and temporal lobes than the left: they push the right temporal lobe altogether aside from the crus cerebri on that side.

*Microscopically.*—The tumour is formed of two apparently different structures. In places there are groups of large, multipolar, and often multinuclear cells with a large nucleus, clearly marked nucleolus, and darkly staining cytoplasm, lying in a matrix of loose tissue which resembles the ground substance of the brain and spinal cord.

In other parts the tumour is composed of a mass of round cells with scanty cytoplasm, and with little or no ground substance, as shown by the ordinary staining methods. Lying around and among these cells are bands and wider strips of fibrous tissue which stains yellowish pink by van Gieson's stain, and is often arranged in short bundles, giving a very similar appearance to that seen in "neuro-fibromata" In this fibrous tissue are seen many cells of the large multipolar type.

When examined by Bielschowsky's method, it is seen that these two apparently different structures are of very similar nature, as everywhere there are darkly staining, clearly cut lines running in all directions through the tissue. These give the staining of nerve fibre processes, and are seen to arise, not only from the large multipolar cells, but also from some of the cells of smaller size. Although they cannot be traced through the cell body as definite fibres, it is seen in specimens which have not been differentiated with acetic acid that the cells which give rise to them are stippled over with dark spots, which other cells do not possess. In differentiated sections this appearance is not seen, and the origin of the nerve fibres is not so definite, as the processes of the cell only stain slightly more darkly than the cell body and it appears that the characteristic black staining is only attained when the fibre has extended some distance away from this. Where it is possible to trace the process for some distance it is seen that it gradually becomes darker, and is collected into a closer strand after extending for about the length of the cell body away from it, but that even at a distance of five times the length of the cell body (about 100 microns) it is still not so dark as the fibres which run near it. In the areas of small round cells the fibres are also numerous, but do not appear to spring from the smallest cells but from small multipolar cells which lie here and there among them. In act the distinction between the appearances of various parts of the tumour is very superficial, as all contain cells which resemble ganglion or motor nerve cells in greater or less numbers.

Weigert-Pal sections show no evidence of the formation of myelin, although here and there it is possible to see myelinated fibres lying by ones and twos. These probably come from cranial nerve roots which have been infiltrated by the tumour.

Nissl staining shows very little. In some of the cells the peripheral area of the cell body stains rather more darkly than the rest of the cytoplasm, and this area has a slightly granular appearance, but nothing resembling a true Nissl granule was seen.

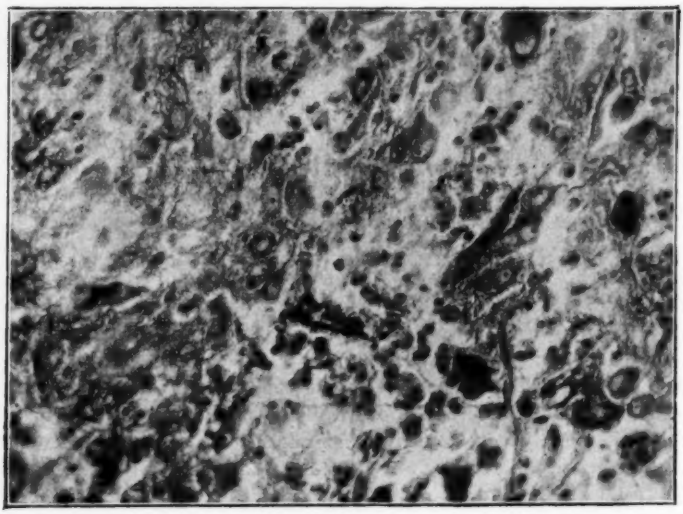

FIG. 30.—Case 34. Mrs. B. Ganglioneuroma. High-power view of ganglion cell area showing numerous black nerve-fibres and nerve-cells. (Bielschowsky's stain. Zeiss 8 mm. obj.)

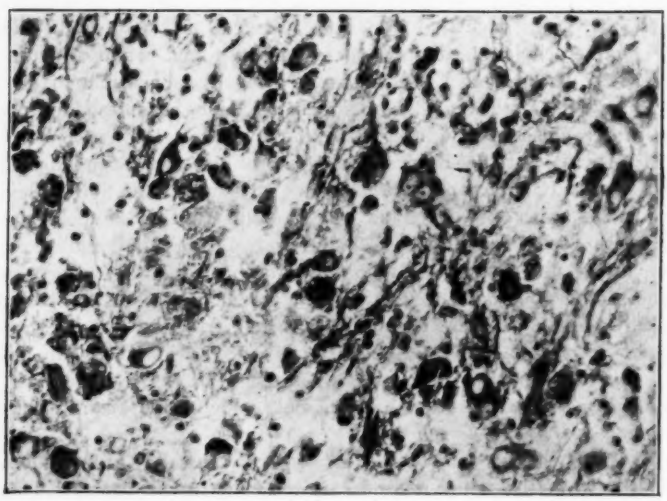

FIG. 31.—Case 34. Mrs. B. Ganglioneuroma. High-power view of ganglion cell area. Note amitotic division of nerve-cells. (Bielschowsky's stain. Zeiss 8 mm. obj.)

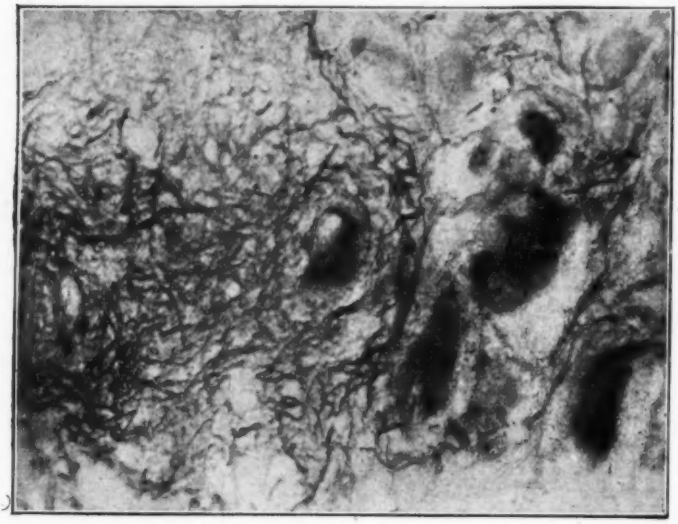

FIG. 32.—Case 34. Mrs. B. Ganglioneuroma. High-power view showing dense network of nerve fibres in a less cellular part of the field. (Bielschowsky's method. Zeiss 8 mm. obj.)

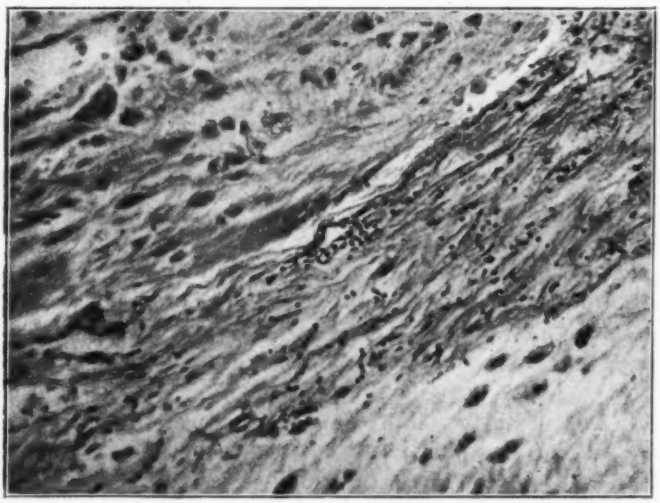

FIG. 33.—Case 34. Mrs. B. Ganglioneuroma. Between two areas of fine nerve-fibres lis nucleated zone of (? sheath) cells. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

The blood-vessels are well formed, the smaller having a definite endothelial lining and being supported by a condensation of tumour tissue, the larger having definite fibrous tissue walls (see figs. 30 to 33).

### Discussion on the Histogenesis of these Neuroblastomata.

In Case 34, in addition to the large nerve cells there are areas composed almost entirely of small round cells. These cells appear to have some connexion with the nerve-fibres, and in places it is possible to trace nerve-fibres to them. Their arrangement and appearance suggest that they are similar to the small round ganglion cells of the retina, cerebellum, &c., and are neurocytes rather than glial cells. The areas formed of these cells give, to some extent, the appearances of a small round-celled sarcoma, but "rosettes" are fairly plentiful in them. In some places they give very similar appearances to those of the tumours in Case 30.

No glial stroma is seen in this tumour, but there are bundles of fibres which resemble closely those seen in neurofibromata, both in their structure and reaction to van Gieson's stain. These stain faintly by Bielschowsky's method, and lose the stain in the differentiation by acetic acid. They are probably sheath cells, which have been described by Falk and others in tumours of this nature. They occur most plentifully in the outer parts of the tumour, where the nerve-fibres tend to run round the circumference, blending with the capsule of the tumour.

Case 33 is undoubtedly a very malignant tumour of the same kind. In this the tendency to degeneration is extreme, so much so that in parts only the layer of cells lying nearest to the blood-vessels retain their shape and staining reaction, the rest of the tumour being debris in process of removal by polymorphonuclear and lymphocytic cells; and at first it was thought impossible to classify the tumour at all, but later sections through less degenerate parts showed the cells to be mainly of large type with long, fleshy processes. Bielschowsky's stain settled the diagnosis in this case, for by its use it was possible to see many undoubted nerve-fibre processes, all twisted and contorted, some very fine indeed, and others thick fibres which could be traced to the large cells. Some of these cells bear a similar relationship to the blood-vessels, as do the large globoid cells in Case 32, although this appearance is less generally seen.

Only a few cells of the small neurocyte type, and no definitely glial cells, can be seen in the central part of the tumour, but the passage

from tumour to healthy brain tissue is marked off by a zone of glial cells, which may be gliomatous in nature (as their close setting suggests) or proliferated glial cells produced by reaction in the normal tissues. There is no attempt at encapsulation of the tumour, and it separates from the brain substance through this glial zone.

Cases 31 and 32 are less definitely neuroblastomata, but their resemblance to one another and the appearance which they had in common with Cases 33 and 34 seemed to justify the diagnosis. In both there are areas of typically gliomatous appearance, and other areas in which large pyriform and conical cells are grouped together, often in relation to blood-vessels.

In Case 32 (fig. 21) this relationship is quite remarkable, many small blood-vessels being outlined by rings of pyriform cells, which seem to be attached to them by a strong process which stains intensely black by Heidenhain's hæmotoxylin, but does not stain so deeply by Bielschowsky's method. Under higher magnification the process is seen to break up into two fibres which run away from one another in contact with or blending with the wall of the vessels. The nucleus of these cells is usually placed eccentrically and is not very large or vesicular, and the nucleolus is not so clearly marked as in Cases 33 and 34, so that it is impossible to say definitely that these are nerve cells, but it is obvious that they are not glial cells, at least not of the more mature types, nor do they, except in their relationship to the wall of a vessel, suggest spongioblasts.

By Bielschowsky's method very few definite black nerve fibres are seen, but no field of the tumour is quite free from them, so that the suggestion that they are old nerve fibres from the invaded brain tissue does not seem to be altogether warranted. Thick fleshy bands which stain more deeply than glial or connective tissue by the silver stain, and which are obviously the same as those which stain intensely black by Heidenhain's hæmatoxylin, are seen to proceed from the globular and pyriform cells, and run in all directions through the field. In their staining reactions these processes are very similar to the nerve processes as they leave the cells in Case 34.

Certain parts of the tumour, especially towards the periphery, are typically gliomatous, but other parts close to the surrounding brain substance are composed of undifferentiated round cells, only a few of which have any obvious processes.

Case 31 is similar in many ways, but appears to be more malignant. Here again the larger cells are grouped together in areas round blood-

vessels. Many of them are elongated cells with one or two nuclei and thick fleshy processes which can be traced away from the cell body for a considerable distance. Their nuclei correspond closely to those of nerve cells of the pyramidal type. Many of them are in process of amitotic division similar to that seen in Cases 33 and 34.

The smaller cells are rounded or elongated, and many of them resemble glial cells, others are quite undifferentiated. Processes considerably thicker than glial fibres run everywhere through the tumour, both among the larger and the smaller cells, but there is no evidence of nerve-fibres by Bielschowsky's method.

This tumour appears to be a connecting link, as it were, between Cases 32 and 33. The large cells resembling nerve cells bear the same relation to the vessels in all three, and are very similar in appearance, arrangements and in methods of cell division in Cases 31 and 33, whereas other parts of the tumour, in Case 31, bear a closer resemblance to Case 32. It is to be noted that the histories in Cases 31 and 33 are very short, which is in accordance with their histological evidences of malignancy.

The points in common between the three tumours briefly are :—

(1) They are unencapsulated but clearly defined tumours of the centrum ovale.

(2) They are composed of two different types of cell, of which the larger have definite thick processes which can be traced some distance from the cell body, and these cells are arranged round blood-vessels with the walls of which some of their processes blend.

Cases 31 to 34 thus give four different pictures of nerve-cell tumours, two of a comparatively benign, and two of a definitely malignant type. Cases 31 and 32 suggest an origin from cells which have not yet been differentiated into neuroblast and spongioblast, but give rise to rudimentary cells of both types. The cells surrounding the vessels in Case 32 are extremely like some of those described in the development of the posterior root ganglion, but retain also a resemblance to glial cells in their nuclei and staining reactions. Cases 33 and 34 are formed of more mature nerve cells, and in neither is there any evidence of glial tissue.

It has been stated that tumours composed of both glial and nerve-cells do not exist, and the supporters of this view would doubtless say that there was no proof that any of the cells in either Case 31 or 32 were definitely nerve-cells, and in this the staining reactions by Bielschowsky's method would support them. The only answer to

this rests in the character of the processes of the large cells, which are fleshier aud longer, and, in fact, more definite than those of any known form of glial cell. And it seems not unlikely that in tumours which owe their origin to undifferentiated cells of the neural epithelium included in the brain matter, and which have some tendency to malignancy, the formation of nerve-cells should be imperfect, so that they show neither Nissl granules nor neurofibrils. It is surely in accordance with all views on tumour formation that a cell which has the potentiality of developing into all forms of nervous and glial cells should give rise to cells unlike any mature form, but resembling both types in some features.

None of the cases in this series showed any myelin sheaths by the Weigert-Pal (Kultschisky-Pal) method; nor did any show definite Nissl granules. All that can be said is that some of the cells retain a faint blue stain round the periphery of their cytoplasm. This is similar to what is described by Dunn as Nissl granules, and it undoubtedly has some relation to them, but it is too slight and indefinite to form a criterion on which to base a diagnosis. This rests in the end, and definitely, on the presence of nerve-fibres (as shown by silver stains), and the relation of these fibres to the cells, although in the absence of this there may be good grounds for assuming that the tumour contains immature nerve-cells.

*Acoustic Nerve-tumours and "Central Neurofibromatosis."*

In the present series there are six tumours of the acoustic nerve, in one of which a bilateral acoustic nerve-tumour was associated with multiple "neuro-fibromata" of the nerve-roots, a central tumour of the cord and a cortical brain tumour. As far as the histology of the tumours is concerned, this case may be treated along with the others, as what differences existed were only slight, and due more to the site of the tumours than their nature.

It may be said at once that these tumours form a class by themselves. Once their histological characteristics are recognized, they should not be mistaken for any other form of tumour with the single exception of the "neurofibromata" of von Recklinghausen's disease, to which they are closely allied.

They are composed of cells which resemble the connective tissue type in having an elongated nucleus and cytoplasm which tails off into a spindle-shaped process at either end, but which differs from it in staining reactions, e.g., with van Gieson's stain, which gives the pro-

cesses more of a brick-red colour than the pure fuchsin staining of connective tissue; thus the ring of fibrous tissue round the vessels is clearly marked off from the cells of the tumour. The cells have a tendency in many places to be arranged in what Cushing has called a "palisade" manner, nucleus lying by nucleus, and cytoplasm by cytoplasm, giving a banded appearance to the section.

In teased specimens, and where the texture is loose, the cell processes can often be seen to split up into two or more fibres after leaving the cell, differing from connective tissue fibres in this as in their greater tendency to degenerative changes.

In addition to these cells, there are areas of a looser texture in which multinucleated cells are common, and the ground substance is formed of small rounded cells with scanty cytoplasm, which tends to run off into several thin, poorly formed processes—a type of cell suggesting myxomatous or glial tissue. The relative proportion of these two different types of tissue varies in different cases, and in different sections from the same case, but usually both are present to some extent. The blood-vessels are usually formed of a definite endothelial lining, with a thin fibrous tissue layer surrounding it. Sometimes the vessel walls show hyaline degeneration. Fatty and mucinous infiltration of the tissue is very common. In the tumours of this series myelinated fibres were extremely scanty, but a few were found in the peripheral parts of the tumour. No nerve-fibres were found by silver staining methods in any of the tumours examined.

The association of bundles of fibrous cells with areas of looser, more reticular tissue, taken along with the staining reaction and arrangement of the fibrous cells, gives a histological picture unlike that of any other tumour. From their histological appearances they have been classed as fibromata, fibroglioma, myxo-sarcoma, and glio-sarcoma, according to the predominating features of the tumour or the whim of the observer. Although areas of fibrous tissue are sometimes seen in them, these are obviously not the essential structure of the tumour, but are probably due to degeneration of tumour cells and replacement by fibrous tissue. For a similar reason cysts are often found. Both these features are shown in the tumour of the cord in Case 35. And an examination of a number of these tumours from the macroscopic point of view is enough to satisfy the observer that in their manner of growth they have little in common with sarcomata, as they do not tend to infiltrate either bone, meninges, or brain tissue. They are usually nodular on the surface, and covered over with a layer of

arachnoid. On section some are granular, and resemble endotheliomata; others show the "watered-silk" appearance seen in fibromata, but of a coarser type, and with a rougher cut surface. Small areas of hæmorrhage and softening are frequently seen.

The following is a case of the rare condition described as

### *Multiple "Central" Neurofibromata.*

*Case* 35.—N. R. S., aged 22 (physician, Dr. Farquhar Buzzard). Admitted March 30, 1917. Died April 11, 1917.

*History.*—There was a gradual onset of symptoms from September, 1916, viz., headache, failing vision, deafness, dragging of the left leg, and then wasting of the left side of the body.

Operation, April 11, 1917. Cerebellar decompression. No tumour found. Patient died shortly after from respiratory failure.

*Macroscopic appearances.*—Brain: (1) A tumour measuring 4·2 by 3·5 by 3·5 cm. is present on the postero-internal border of the left occipital lobe, immediately above the calcarine fissure. This is fairly soft and covered by felted pia-mater.

(2) A tumour of about the same size, firmer, nodular and of a glistening surface, is found in the right cerebello-pontine angle.

(3) There is a similar tumour 3 by 2 by 1·6 cm. in the left cerebello-pontine angle.

(4) The whole cervical region of the cord contains a central tumour which causes great enlargement, the greatest measurement being 2·5 cm. transversely. On section of the cord at this level, the tumour is seen to extend the length of the cervical region, with cavity formation in its centre. This is somewhat irregular, but lies usually towards the centre of the cord, rather to one side. In some places there is no cavity, e.g., towards the upper end of the cervical region, but a rounded mass fills the centre of the cord, and above and below the tumour a smaller cavity runs up and down in the region of the posterior horn on one side; whereas the rest of the cord appears normal.

(5) Many of the nerve-roots, both anterior and posterior, are enlarged into fusiform swellings. On careful examination it can be seen that this process is almost universal, but some of the swellings are very minute. There is, however, a larger swelling about 1 cm. in diameter on the left side of the cervical enlargement, at the level of the tumour, which has flattened out the side of the cord.

Microscopically these tumours are all of very similar character, their cells being mostly fusiform, and resembling fibroblasts, but staining a brownish red with van Gieson's stain, and thus standing in sharp colour contrast to fibres of connective tissue round blood-vessels. The cell fibres are fairly thick and are arranged in loose bundles or whorls, often showing the palisade arrangement of nuclei and cytoplasm, which is seen in Case 40. This is seen especially well in

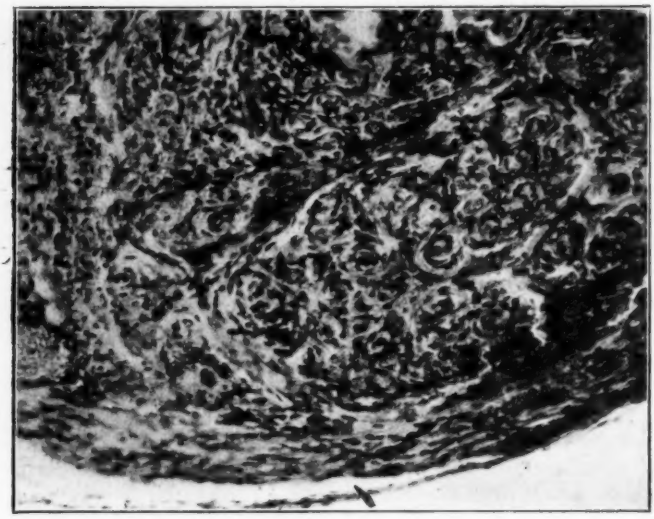

FIG. 34.—Case 35. N. R. S. Multiple central neurofibromata. Emerging nerve-roots just below central tumour of the cord showing the earliest stages of neurofibromatosis.

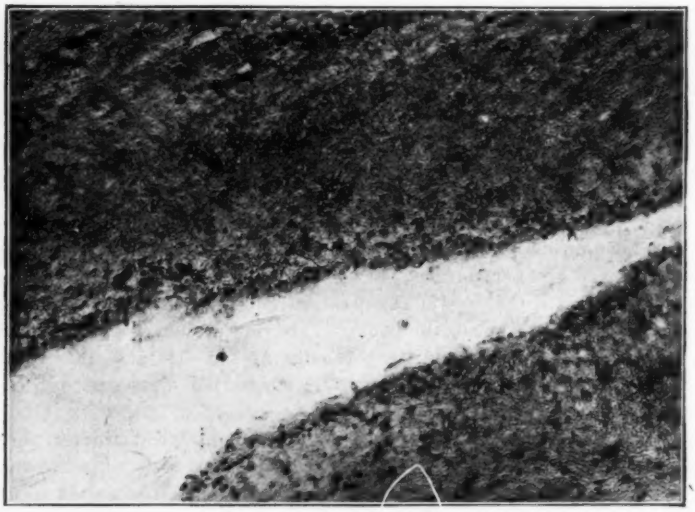

FIG. 35.—Case 35. N. R. S. Multiple central neurofibromata. Wall of cavity below tumour of cord showing slight glial increase in innermost layer. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

the central tumour of the cord and also in the large tumour lying at the side of the cervical enlargement (see fig. 38).

In some places the cells are more rounded with relatively little cytoplasm and at first sight resemble lymphocytes, but their cytoplasm is prolonged into fine processes which run a considerable distance from the cell body. There is everywhere a tendency to œdema, as shown by the separation of bundles and cells. The blood-vessels are for the most part well formed, their walls being formed of an endothelial lining and a definite fibrous tissue coat.

In the central tumour of the cord there is in parts a great formation of dense fibrous tissue, in rounded masses which are ringed round by masses of tumour cells. This is not seen in any of the other tumours either round the brain-stem or cord, and may be due to a starvation of blood supply in this central tumour. In the ponto-cerebellar angle tumours the blood-vessels are much more poorly formed than in the tumours of the cord, being simply outlined by endothelial cells. They show more tendency to œdema than the cord tumours.

The tumour in the cervical region of the cord is surrounded by a zone of extreme glial proliferation with the formation of enormous glial cells with a large cell body which is prolonged into thick processes which can be traced for a considerable distance. Some of these cells are multinucleated. The cavities in the cord are also ringed by a glial layer, the innermost layer of which contains a larger number of nuclei than is seen elsewhere, but this cell increase is not nearly so great as in parts of the subpial layer, both in the cervical and dorsal regions of the cord. It is seen also in the posterior longitudinal fissure in the upper dorsal region, just below the level at which the fissure reappears after having been lost as a result of the tumour in the centre of the cord. At this level there is a very small extension of this central tumour, shown as a collection of rounded cells with darkly stained nuclei, lying in the posterior horn on one side. This has no connexion with the central canal of the cord, nor does it reach to the cord surface (see figs. 35 to 37).

The subpial cell increase seems to have some relation to the emergence of the posterior nerve-roots, being, in places, most marked close to them, but it is extremely patchy, and is seen sometimes on the posterior surface and sometimes on the lateral surface of the cord.

Very many of the nerve roots are in a more or less advanced stage of "neurofibromatosis," some showing the very earliest changes; and in these it seems to be possible to verify the contention of Durante, Verocay, and others, that the tumours arise from overgrowth of the cells of the neurilemma sheath of Schwann, as concentric layers of cells are seen surrounding the nerve-fibre and encroaching on its tube, so that there appears to be no room for anything but the axis-cylinder. In longitudinal sections of nerve-roots stained by iron-alum hæmatoxylin or by the Kultschitsky-Pal method, it is seen that the myelin sheath is lost in these constricted tubes, but they are seen to regain their myelin after leaving the tumour (see fig. 34).

By the Kultschitsky-Pal method it is not possible to make out any new formation of myelinated fibres, although a very few such fibres can be seen

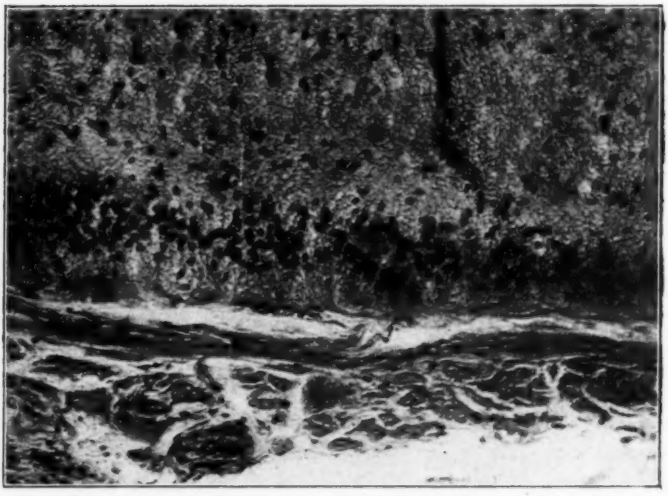

FIG. 36.—Case 35. N. R. S. Multiple central neurofibromata. Showing subpial gliosis close to point of emergence of posterior nerve-root. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

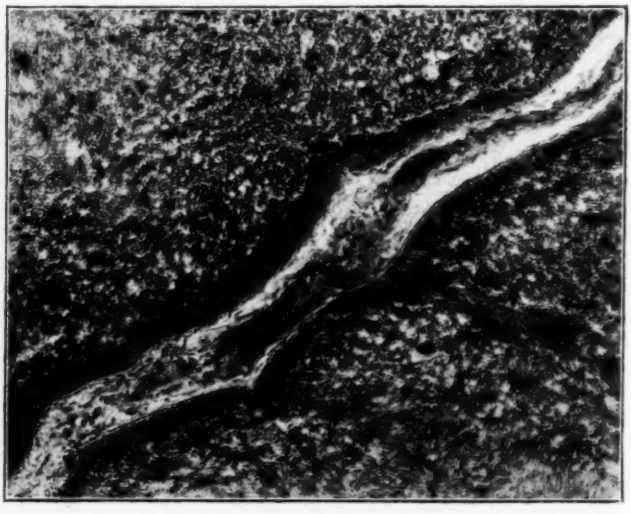

FIG. 37.—Case 35. N. R. S. Multiple central neurofibromata. Postero-median fissure below level of tumour of cord showing subpial gliosis. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

in the peripheral parts of the ponto-cerebellar angle tumours. In the central tumour of the cord there are areas, especially between the tumour and the cavity in the cervical cord, where lines of very fine myelin traverse the cord from one side to the other. These may be new myelin, as their fine, beaded appearance suggests, but it is probable that they are in that case formed round pre-existing axis cylinders which have survived the pressure of the tumour. Droplets which stain black by this method, and which resemble the droplets of broken-down myelin seen in a degenerated nerve, are very plentiful in the tumours of the ponto-cerebellar angle.

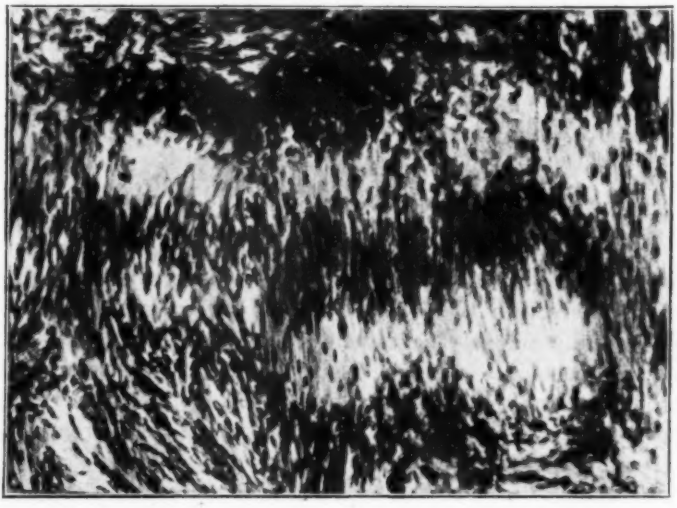

FIG. 38.—Case 35. N. R. S. Multiple central neurofibromata. Tumour of cord showing "palisade" arrangement of cell nuclei. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

It is to be noted that microscopically the cavity is seen in all sections of the cervical cord, but is small at the level of most fibrous tissue formation. At one point the wall of the cavity is encroached on by the tumour, and tumour cells project a short distance into its lumen, but for the most part the tumour is distinct from the cavity.

*The tumour of the occipital cortex* differs from the others to some extent, chiefly in the amount of fibrous tissue present, and in the formation of "psammomatous" granules. These are seen to be formed from globular condensations of the fibrous tissue and the deposition of calcareous salts in these. The fibres forming the main ground mass of the tumour run for the most part straight, and are not arranged in a concentric manner round the psammoma granules. On the whole there is less tendency to whorl formation than in some of the other tumours of the same case. The blood-vessels are

better supported by connective tissue fibres than in the tumours of the acoustic nerve, and everywhere there is an excess of connective tissue, fine fibres, which take a pink stain with Van Gieson's fluid, lying between the brown staining fibres.

Although the appearances are to some extent suggestive of an endothelioma, the resemblance to the other tumours found in this case is very much closer, and there are several points in which it differs from the other endothelioma of this series.

In the first place the blood-vessels are not formed of the same tissue as the main substance of the tumour, but are always surrounded by a clearly defined layer of pink-staining fibrous tissue. There are none of the small vessels running between the cells of the tumour which are characteristic of endotheliomata.

There is also a greater distinction between the elongated brown-staining cells composing the tumour and the connective tissue fibres, and less tendency to whorl formation than was seen in the other endotheliomata.

## Discussion of the Histogenesis of Acoustic Nerve Tumours.

In his recent monograph Cushing has investigated fully the point of origin of these tumours from the acoustic nerve, and considers that it usually lies within the internal auditory meatus which is always enlarged on the side of the tumour. In a case examined after this series was concluded I was able to examine the petrous temporal bones on both sides, and found the internal auditory meatus widened out anteriorly on the side of the tumour, the foramen being prolonged as a wide depression on the surface of the bone.

The relationship of the tumour cells to the nerve elements from which they arise has been the subject of considerable controversy which cannot yet be considered as definitely settled. In the light of the collected cases of multiple neurofibromatosis, either "central" or generalized, associated with tumours of the acoustic nerve, it must be considered that tumours of the acoustic nerve are closely akin to the peripheral nerve tumours of von Recklinghausen's disease, differing from them only in their greater tendency to the formation of glia-like areas, and in the absence or extreme scarcity of myelinated or bare nerve-fibres. In all probability the bundles of fibrous cells are similar in all these tumours and have a similar origin.

In this connexion it is interesting to recall the *history of the subject.*

The histology of the tumours was first observed by Virchow, who considered them to be neuromata.

But in 1881 von Recklinghausen, noting their association with

"molluscum fibrosum," named them at first "neurofibromata" as meaning "fibromata in the substance of nerves," but later realizing that the term was incorrect, and regarding them as formed from the endoneurium, he changed their name to "multiple fibromata." However, the earlier name stuck and obtained general currency.

Pierre Marie, in 1896, considered that the tumours of the nerves and of the skin were different in nature, the former arising from the sheath cells, the latter from the fibrous tissue of the skin.

In 1900 Alexis Thomson reviewed the subject and considered that the tumours sprung from the endoneurium. He noted the constancy of the histological picture in molluscum fibrosum, in multiple neurofibromata, and in plexiform neuromata of nerves.

Durante in 1907 considered that the tumour arose from proliferation of the sheath cells, or, as he calls them, the "cellules segmentaires," which, according to his view, formed the axis cylinder, and he named the tumours "névromes vraies segmentaires." He noted also the presence of "large polygonal multinucleated cells" and "stellate cells with elongated nucleus" in the more "myxomatous" parts of the tumour. This corresponds closely with the appearances seen in tumours of the acoustic nerve.

In 1910 Verocay reviewed the subject in the light of two cases of multiple neurofibromata associated with gliomata of the cord, tumours of the dura mater and acoustic nerve tumours. He considered as most unlikely the supposition that tumours arising from the fibrous tissue in nerves could show such great differences in their general pathology and histology from tumours of other connective tissues, and held that the cells composing "neurofibromata" were undifferentiated peripheral neurocytes, capable of giving rise to ganglion or to glial cells or to cells of the sheath of Schwann. The tumours of the acoustic nerve he considered to be in their histological characteristics cellular "neurofibromata." He called all these forms of tumour "Neurinomata" (nerve-thread tumours). He differed from Durante in his interpretation of the rôle of the sheath of Schwann, which he considers to have the functions of forming a channel along which the nerve-fibre may travel and of subserving its nutrition. The sheath of Schwann is thus analogous to the glial tissue of the central nervous system.

It is true that the cells of acoustic nerve tumours do not give the special staining of the sheath of Schwann, but this is discounted by the fact that we are dealing with imperfectly formed tumour tissue. Nor are glial fibres found at all generally in these tumours, though Cushing

figures a few fibres which give the specific staining reactions to Mallory's neuroglia stain.

This theory of origin has certainly much to support it, and provides an explanation for certain cases of multiple tumours of nerves, nerve roots, and central nervous system.

Cushing (1917) considers that the tumours of the acoustic nerve arise from undifferentiated cells at the junction of the glial elements with the sheath of Schwann. This takes place at a considerable distance from the brain stem, which is probably greater in the vestibular than in

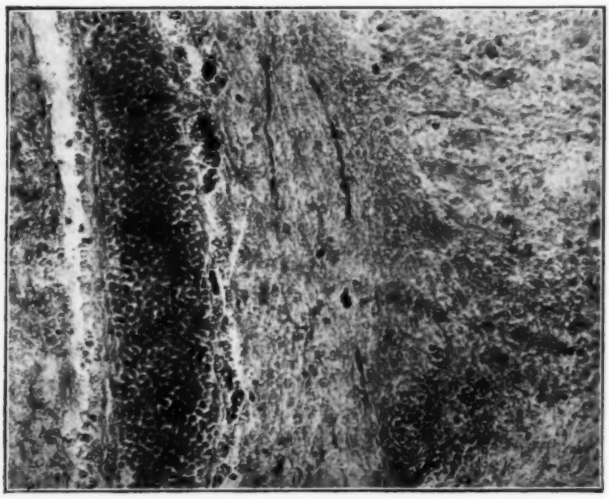

FIG. 39.—Case 36. G. M. Acoustic nerve tumour. Showing two myelinated fibres running in the neighbourhood of a vessel. (Kultschitsky-Pal. Zeiss 16 mm. obj.)

the cochlear nerve. This "transition zone" is probably an area of unstable equilibrium, and may be more so in the eighth nerve than in the other cranial and spinal nerve roots, as it is to be noted that most cases of multiple tumours of the nerve roots ("central neurofibromatosis") are associated with bilateral acoustic nerve tumours (see Case 35). In Verocay's cases, and in one of Cushing's cases, ganglion cells were found in acoustic nerve tumours. These had been observed by earlier writers, but were usually considered to be pre-existing ganglion cells in relation to the eighth nerve. Verocay, however, considers them to be an integral part of the tumours, and with this view Cushing assents.

That the multiple tumours of the nerve roots in Case 35 are derived from the cells of the sheath of Schwann seems capable of ocular demonstration, as there is obvious proliferation of cells in concentric rings right in to the nerve root and encroaching on the lumen of the tube so as to cause disappearance of the myelin sheath. The axis cylinder is seen in the centre, closely surrounded by the "signet ring" of the innermost proliferated layer, and no line of tissue can be seen between axis cylinder and "signet ring."

The increase of cells in the subpial layer of glia is of great interest in this case, as suggesting that the tendency to proliferation had affected them as well as the innermost layer of the sheath of Schwann. But it is to be noted that the central tumour of the cord is formed of fibrous cells similar to those of the acoustic nerve tumours. It may be assumed that it has arisen from included elements which should have migrated to form the syncytium of the sheath of Schwann.

It is impossible to avoid the suggestion that certain "psammomata," as well as some tumours which have been described as "endotheliomata," are of the same origin as acoustic nerve tumours. To the writer it appears clear that the large cortical tumour in Case 35 is of the same nature as the other tumours in the case, although it is certainly a psammoma, and has certain points of resemblance to the endotheliomata.

It is also probable that certain of the cases of multiple psammomata in relation to the nerve roots are neurofibromatous in origin. The tendency which tumours of the acoustic nerve show to hyaline degeneration of the vessel walls is well shown in Cushing's monograph and the resulting impoverishment of the blood supply may result in fibrosis and the deposition of calcareous salts in the fibrous tissue.

While it is unjustifiable without greater knowledge to assume that the tumours of the cortex in Verocay's case were of the same nature, it seems *prima facie* more probable than when the majority of the tumours in a case conform to one type, the others, though somewhat dissimilar in histological appearances, should, at any rate, arise from the same embryonic layer, and possibly also from undifferentiated cells of a similar type.

Generalized or "central" neurofibromatosis usually commences fairly early in life, whereas single acoustic nerve tumours are rarely

met with before the end of the third decade. In a similar manner both cases of multiple gliomata in this series occurred during the second decade, while single gliomata were not met with before the third decade. This is as would be expected on the supposition that these tumours of the nervous system arise from some area of unstable equilibrium or developmental abnormality. In some of them this hypothesis seems to be warranted by the development of multiple growths at or near to the "transition zone" of nerve roots, or by the presence in the tumour of two or more different types of nervous

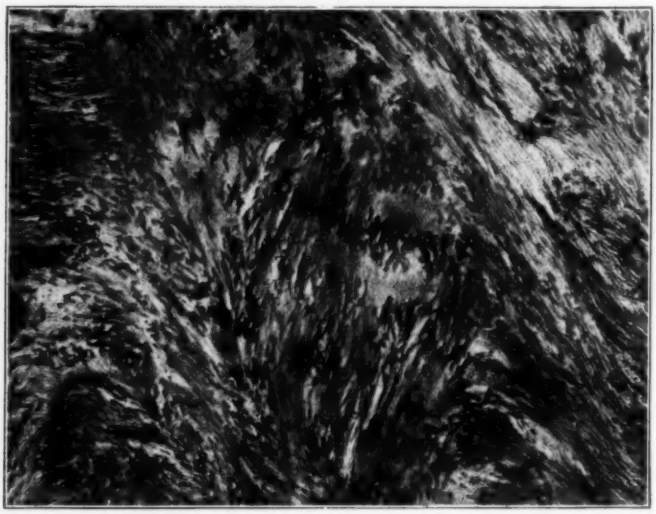

FIG. 40.—Case 40. H. P. Acoustic nerve tumour. Showing "palisade" arrangement of nuclei. Compare with fig. 38. (Hæm. v. Gieson. Zeiss 16 mm. obj.)

tissue. For while it is conceivable that adult glial tissue under the stimulus of some irritant or "diminished external resistance" might proliferate to form a neoplasm, it seems less likely that mature nerve cells would behave in this way. Still less probable is it that a mature cell of either kind would retrace its steps in development so as to give rise both to undifferentiated cells, and to cells of the nerve cell and glia cell type. It seems most plausible therefore to assume that tumours which give rise to more than one type of nervous tissue are developed from some undifferentiated neurocyte, which, either owing to lack of function (Adami), or from some

other cause, takes on a "habit of growth." That such cells are commonly present in the "transition zone" of the nerve roots is also suggested by the cases of multiple growths in this region, and it is probable that a fuller study of the histology of the nerve root may shed more light on the etiology of tumours of nervous tissue.

In conclusion I wish to express my thanks to the Medical Research Committee, by whose help I was enabled to carry out this examination.

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# THE CEREBROSPINAL FLUID IN HERPES ZOSTER, AND THE RELATION OF HERPES ZOSTER TO SYPHILIS.

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THIS short paper is the outcome of investigations that were being made on the cerebrospinal fluid in syphilis, in all its phases. While the patients were under actual treatment for syphilis with "606," or under observation for a long period thereafter, a number developed herpes zoster. The following questions in consequence arose :—

(1) Was the cerebrospinal fluid affected in any way in herpes zoster either in non-syphilitic or syphilitic subjects?

(2) Was there any relation between syphilis and herpes zoster?

(3) Had the administration of "606" anything to do with the development of herpes zoster?

Since Head and Campbell [2] published their epoch-making researches on the pathological changes in the posterior root ganglia, &c., in herpes zoster, little or no advance has been made as regards the etiology of this condition. During the last few years several interesting papers [3] have been published drawing attention to the possible relationship between herpes zoster and chicken-pox [5] and even their possible common origin. A large number of instances have been cited where there has been the curious incidence of chicken-pox in families after one, usually an adult member, had suffered from herpes zoster, and vice versa ; also a few cases where the two diseases occurred in the same individual at one and the same time. Otherwise the etiology of herpes zoster remains a mystery, though everything points to a microbic origin.

With such profound inflammatory changes occurring in the posterior root ganglia, and secondary degenerative changes in the posterior roots and posterior column of the spinal cord in herpes zoster, it would not be surprising to find some pathological changes in the cerebrospinal fluid, due to some reaction on the part of the meninges.

## The Cerebrospinal Fluid.

This was examined chiefly with reference to (1) the cellular elements; (2) albumen; (3) globulin, and (4) Wassermann reaction.

For estimating the lymphocytosis, Rosenthal's and Nageotte's counting chambers were used.

As far as can be ascertained very few investigations have been made. Several French authors record very briefly a few cases but give no details regarding the numerical estimation of the cell contents. Lochelongue [4] simply states that there is usually no lymphocytosis, and if so, very slight; a statement not at all in keeping with our observations. Milian [7] states that the cellular contents are very inconstant. Achard and Lanbry [1] examined seventeen cases; in eight cases the lymphocytosis results were negative, and in the remainder very slight.

The cell contents were estimated without centrifugalizing the cerebrospinal fluid. Normal cerebrospinal fluid is practically devoid of cellular elements, except an occasional lymphocyte and epithelial cell; anything above two lymphocytes per c.mm. we have taken as abnormal. We may here state that the question of the patients being syphilitic or non-syphilitic subjects does not affect the findings in the cerebrospinal fluid. The majority of the observations were made in non-syphilitic subjects. The accompanying tables give the details of the cases—the following is a brief résumé.

(1) *The cellular elements.*—In forty-two cases the cytological estimation was made with extremely striking but inconstant and puzzling results. In the great majority of the cases (28) there was some degree of lymphocytosis, but this varied enormously, from normal (1 or 2 lymphocytes) to an intense lymphocytosis (470 per c.mm.). In ten cases the counts registered over 50 cells per c.mm. We could find no adequate explanation for these great differences. There was absolutely no relation to the intensity of the eruption as one might perhaps have expected—rather the reverse. On the whole, the highest estimates were found in those cases with a very slight abortive eruption, e.g., three such cases gave counts respectively of 136, 350 and 52 per c.mm. On the other hand, some cases with a mild eruption gave normal counts. Similarly, in cases where the eruption was extensive and acute, the lymphocytosis varied in an extraordinary way, from practically normal to a cell count of 200 per c.mm. In ten cases the counts registered within normal limits.

Neither could these results be accounted for by the examination being made at different stages, nor the age or general condition of the patient explain in any way the discrepancy.

In seven cases a second examination of the cerebrospinal fluid was made, from two to three weeks after; all showed a considerable diminution in the cell counts, as follows:—

| | | | | |
|---|---|---|---|---|
| Case I. | A mild abortive form .. | 1st examination | = 136 | cells per c.mm. |
| | | 2nd ,, (3 weeks later) | = 5 | ,, |
| Case II. | A very acute herpes zoster of the trigeminal nerve | 1st examination | = 100 | ,, |
| | | 2nd ,, (1 month later) | = 40 | ,, |
| Case III. | Acute thoracic zoster .. | 1st examination | = 200 | ,, |
| | | 2nd ,, (16 days later) | = 18 | ,, |
| Case IV. | | 1st examination | = 470 | ,, |
| | | 2nd ,, | = 42 | ,, |
| Case V. | | 1st examination | = 11·8 | ,, |
| | | 2nd ,, | = 2·4 | ,, |
| Case VI. | | | | |

The lymphocytes were mainly of the small variety, but up to 25 per cent. large lymphocytes were found in some cases. No polymorphonuclear leucocytes were differentiated.

(2) *Albumen.*—This was estimated by Sicard's method. This consists of a long narrow graduated tube in which 4 c.c. of cerebrospinal fluid are raised to almost boiling point and then twelve drops of 1 per cent. trichloral-acetic acid added. The precipitate is read off six hours later. Though not a very accurate method, it is practical from the clinical point of view. Some of the tubes we found were not calibrated and graduated exactly alike, which consequently appreciably altered the accuracy of the readings. No constant change was found. In the majority of cases there was a slight increase, and in two cases in which there was a marked lymphocytosis (470 and 350 per c.mm.) the albumen registered double the normal quantity, viz., 42 and 56 centigrammes. The normal amount is regarded as being from 22 to 28 centigrammes.

(3) *Globulin.*—The presence of globulin was tested for by the Nonne-Apelt method, which consists in floating the cerebrospinal fluid on a solution of sulphate of ammonia. A fine opalescent ring indicates the globulin. In one case only was there a clear decided ring, namely, the case with the high lymphocytosis (350) and greatly increased amount of albumen (56 centigrammes).

(4) *Wassermann reaction.*—It was thought better to keep the authors' figures separate regarding this point, as the observations were

made under different conditions. One of us (Captain Brown) had charge of a large skin division attached to a venereal hospital, the other (Dr. Dujardin) was in charge of the syphilis section at the Belgian Base.

TABLE I.—Captain Brown's Cases.

| Case | Region | Remarks | Cells | Albumen | Wassermann | |
|---|---|---|---|---|---|---|
| | | | | | C.S.F. | Blood |
| | | | | Centigr. | | |
| 1 | Supra-orbital | An acute case .. .. .. | 9 | 40 | Neg. | Neg. |
| 2 | Trigeminal .. | Very acute case .. .. .. | 100 | .. | ,, | ,, |
| | | 2nd examination 1 month later.. | 40 | .. | ,, | ,, |
| 3 | Cervical .. | Acute eruption .. .. .. | 7 | 40 | .. | .. |
| 4 | ,, .. | Acute. Recent syphilitic .. | 2 | 40 | Neg. | Neg. |
| 5 | Dorsal .. | .. .. .. .. .. | 3 | .. | .. | .. |
| 6 | ,, .. | Acute .. .. .. .. | 126 | 25 | Neg. | Neg. |
| 7 | ,, .. | .. .. .. .. .. | 47 | .. | .. | .. |
| 8 | ,, .. | Mild abortive eruption .. .. | 136 | .. | Neg. | .. |
| | | 2nd examination 3 weeks later.. | 5 | .. | ,, | .. |
| 9 | ,, .. | .. .. .. .. .. | 9 | .. | .. | .. |
| 10 | ,, .. | Acute eruption .. .. .. | 3 | 25 | Neg. | Neg. |
| 11 | ,, .. | .. .. .. .. .. | 7 | 25 | .. | .. |
| 12 | ,, .. | Very slight eruption .. .. | 52 | 25 | Neg. | Neg. |
| 13 | ,, .. | Eruption fading 16th day .. | 1 | 22 | ,, | .. |
| 14 | ,, .. | Slight eruption .. .. .. | 1 | 25 | ,, | Neg. |
| 15 | ,, .. | ,, ,, .. .. .. | 0·5 | 22 | ,, | ,, |
| 16 | ,, .. | Slight abortive eruption.. .. | 350 | 56 | ,, | ,, |
| 17 | 11th dorsal .. | Very acute .. .. .. .. | 200 | 40 | ,, | ,, |
| | | 2nd examination 16 days later .. | 18 | 35 | ,, | ,, |
| 18 | Lumbar .. | Very slight case .. .. .. | 1 | 40 | .. | .. |
| 19 | ,, .. | Mild case .. .. .. .. | 0·5 | 22 | .. | .. |
| 20 | ,, .. | ,, ,, .. .. .. .. | 5 | 15 | .. | .. |
| 21 | ,, .. | .. .. .. .. .. | 66 | .. | .. | .. |
| 22 | ,, .. | Acute. Syphilitic c iritis .. | 7 | 45 | Neg. | Neg. |
| 23 | Sacral .. | .. .. .. .. .. | 45 | 35 | .. | .. |
| 24 | ,, .. | .. .. .. .. .. | 5 | 22 | .. | .. |
| 25 | ,, .. | .. .. .. .. .. | 20 | 40 | .. | .. |

TABLE II.—Dr. Dujardin's Cases.

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | Cervical .. | Latent syphilitic. Recent .. | .. | .. | .. | .. |
| 2 | ,, .. | Old syphilis of seven years .. | 0 | .. | Neg. | Neg. |
| 3 | Thoracic .. | Recent secondary syphilis .. | 11·8 | 22 | ,, | Pos. |
| 4 | ,, .. | ,, ,, ,, .. | 10 | .. | ,, | .. |
| 5 | ,, .. | ,, ,, ,, .. | 2·5 | .. | .. | .. |
| 6 | Abdominal .. | Tabes very marked .. .. | 40·8 | 50 | .. | .. |
| 7 | ,, .. | Marked tabes .. .. .. | 88 | 22 | .. | .. |
| 8 | ,, .. | Very marked tabes .. .. | 32 | 50 | Pos. | Pos. |
| 9 | ,, .. | Recent syphilis .. .. .. | 4 | .. | .. | .. |
| 10 | ,, .. | ,, ,, .. .. .. | .. | .. | .. | .. |
| 11 | ,, .. | ,, ,, .. .. .. | .. | .. | .. | .. |
| 12 | Lumbar .. | ,, ,, Neuro-recidive.. | 92·8 | 2 | .. | Pos. |
| 13 | ,, .. | Primary. After first injection of neo-salvarsan | 246 | 30 | .. | Pos. |
| | | 2nd examination 8 weeks later.. | 15·2 | .. | .. | Pos. |
| | | Non-Syphilitic Cases. | | | | |
| 14 | Occipital .. | Slight eruption .. .. .. | 470 | 42 | Neg. | Neg. |
| 15 | Cervical .. | ,, ,, .. .. .. | 1·2 | .. | ,, | ,, |
| 16 | Abdominal .. | Acute eruption .. .. .. | 18 | .. | .. | .. |

(Captain Brown's Figures.)

In twelve cases of herpes zoster in which the question of syphilis was thoroughly inquired into and Wassermann test carefully done in both blood and cerebrospinal fever only two had had syphilis. The Wassermann tests were negative, but both had been treated for primary syphilis a short time previously in this hospital. A third case was possibly syphilitic, presenting a suspicious Argyll-Robertson pupil.

Major C. White, R.A.M.C., who is in charge of the syphilis division, and who has passed through his hands about 19,000 cases of syphilis, has kindly stated that he cannot recall having seen more than two cases of herpes zoster occurring during the treatment with salvarsan or neo-salvarsan. These patients after being discharged from hospital go to their units, &c., and consequently a herpes zoster, which is more likely to develop some time after treatment, would pass through a different channel. The interesting point, however, is the rarity of herpes zoster occurring during the course of arsenical treatment.

(Dr. Dujardin's Statistics.)

The striking feature of this series of cases is the frequent incidence of herpes zoster among syphilitic subjects. These cases were collected from among the soldiers and civilians presenting themselves for medical advice at the Belgian Base Military Hospital, and, being a garrison depot, the population was more or less stationary, and the patients consequently could be kept under observation. Within two years about 1,200 cases of syphilis in one stage or another appeared, and out of this number nine cases of herpes zoster developed thereafter, i.e., approximately 4 per 1,000 per annum. Among about 13,000 other patients only ten cases of herpes zoster were seen, i.e., less than 1 per 1,000.

It would seem therefore that there was a predisposition to herpes zoster in syphilitic subjects. This predisposition appeared more striking in the work of Head and Campbell [2]. In their investigation of twenty-one cases, which was made from a pathological point and without any preconceived ideas on the present subject, we find that fourteen of their cases were certainly syphilitics; other four probably syphilitic, i.e., more than two-thirds of the cases.

In all, sixteen cases were investigated; thirteen occurred in syphilitic subjects, three in non-syphilitic. Of these thirteen patients, ten had received arsenical treatment (neo-salvarsan) some weeks or months prior to the appearance of the herpes zoster: in two cases of primary syphilis the herpes zoster developed during the course of treatment,

viz., after three injections of neo-salvarsan. One patient had had no previous arsenical treatment. There was one instance of herpes zoster (of lower abdomen) developing practically at the same time as a syphilitic nervous lesion; the following is a résumé of the case. The patient was an early case of tabes, with Argyll-Robertson pupil and lightning pains, and giving a history of syphilis ten years previously. Examination of the cerebrospinal fever revealed a lymphocytosis of 15 cells per c.mm. albumen normal. Three injections of novarseno-benzol (30, 45, 60° C.) were given at eight days' interval. Three weeks after the last injection the abdominal herpes appeared, and three weeks after the herpes an external oculo-motor paralysis of the left eye. A second examination of the cerebrospinal fever at this time revealed a lymphocytosis of 85 cells per c.mm.

With regard to the nature of this predisposition one can readily admit that the meningeal reaction, which is present more or less in the majority of syphilitic subjects (especially after the primary stage), will naturally open the road to infection by the still unknown organism of herpes zoster. In addition, an inefficient arsenical treatment might under certain circumstances accentuate, some time later, this same syphilitic meningeal reaction, and hence reinforce this predisposition to herpes zoster.

It would seem also, from the figures in Table II, that in syphilitic subjects the herpes zoster has a predilection for the lumbar and sacral ganglia, just as the lower spinal regions are more frequently attacked in syphilitic meningitis (cf. the relative frequency of tabes affecting the lower limbs and tabes affecting the upper limbs).

Conversely, in a case of herpes zoster the possibility of a prior syphilitic infection must be considered, more especially so if the herpes involves the lower spinal ganglia.

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